IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ADVANCED CARDIOVASCULAR SYSTEMS, INC.,	)	Civil Action No.
Plaintiffs,	)	
v.	)	**JURY TRIAL DEMANDED**
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

COMPLAINT FOR DECLARATORY JUDGMENT OF PATENT INVALIDITY AND NONINFRINGEMENT

Plaintiffs Abbott Laboratories and Advanced Cardiovascular Systems, Inc. (collectively "Abbott") bring this Complaint against Defendants Johnson and Johnson, Inc. and Cordis Corporation (collectively "J&J"). This is an action for a declaratory judgment and injunctive relief that United States Patent No. 6,585,764 entitled "Stent With Therapeutically Active Dosage Of Rapamycin Coated Thereon" (the "Wright '764 patent"), United States Patent No. 6,808,536 entitled "Stent Containing Rapamycin Or Its Analogs Using A Modified Stent" (the "Wright '536 patent"), and United States Patent No. 6,776,796 entitled "Antiinflammatory Drug Delivery Device" (the "Falotico '796 patent") are invalid and not infringed by Abbott. The Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent are attached as Exhibits A – C, respectively. Abbott alleges as follows:

THE PARTIES

1. Abbott Laboratories is a corporation organized under the laws of the State of Illinois and has a principal place of business at 100 Abbott Park Road, North Chicago, Illinois.

2. Advanced Cardiovascular Systems, Inc. ("ACS") is a corporation organized under the laws of the State of California and has a principal place of business at 3200 Lakeside Drive, Santa Clara, California. ACS is a subsidiary of Abbott Laboratories.

3. On information and belief, Johnson and Johnson, Inc. is a corporation organized under the laws of the State of New Jersey and has a principal place of business at One Johnson and Johnson Plaza, New Brunswick, New Jersey.

4. On information and belief, Cordis Corporation ("Cordis") is a corporation organized under the laws of the State of Florida and has a principal place of business in Miami Lakes, Florida. Cordis is a subsidiary of Johnson and Johnson, Inc.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States (35 U.S.C. § 1 *et seq.*).

6. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

7. This Court has personal jurisdiction, general and specific, over J&J.

8. On information and belief, J&J has systematic and continuous contacts in this judicial district.

9. On information and belief, J&J regularly avails itself of the benefits of this judicial district, including the jurisdiction of the courts.

10. On information and belief, J&J regularly transacts business within this judicial district.

11. On information and belief, J&J regularly sells products in this judicial district. J&J derives substantial revenues from sales in this district.

12. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

BACKGROUND

13. J&J, and in particular Cordis, directly competes with Abbott in the field of intravascular stents used to treat coronary artery disease.

14. The coronary stent industry is highly litigious. J&J, and in particular Cordis, has a well-known history of suing competitors in this field for patent infringement.

15. On three occasions within the last ten years, Cordis sued ACS in this district, alleging patent infringement. (*Cordis Corporation, et al v. Advanced Cardiovascular Systems, Inc, et al.*, C.A. No. 97-550-SLR; *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 97-635-SLR; and *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 98-065-SLR).

16. In early 2006, J&J and Boston Scientific Corporation ("BSC") each were bidding to acquire assets of Guidant Corporation ("Guidant"), which at the time was the parent corporation of ACS. In conjunction with BSC's bid, ACS would be acquired by Abbott Laboratories, which was the ultimate result.

17. One of the key assets of ACS was the XIENCE V drug eluting stent system ("XIENCE V"), which elutes a proprietary drug known as everolimus. ACS holds an exclusive patent license to use everolimus for drug eluting stents. In clinical trials, everolimus has proven superior to other drugs.

18. On information and belief, J&J believed in early 2006 that the XIENCE V would be launched within a few months.

J&J's Public Threats To Sue For Patent Infringement By XIENCE V

19. On information and belief, J&J undertook a public campaign to cast a cloud over the launch of the XIENCE V.

20. On information and belief, as a main thrust of this public campaign, J&J alleged that the XIENCE V would infringe patents allegedly owned by J&J and that J&J would sue Abbott for infringement by the XIENCE V following its launch. On information and belief, J&J's allegations related to at least the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

21. On information and belief, J&J broadcasted threatening statements to industry analysts regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

22. For example, the Prudential Equity Group, LLC published a report on January 20, 2006, titled "JNJ: Takes Off The Gloves In Its Fight With Boston Scientific For Guidant," attached as Exhibit D ("the Prudential report"). In the Prudential report, parties are identified by their stock symbols: ABT for Abbott, GDT for Guidant, JNJ for J&J, and BSX for BSC.

23. On information and belief, the Prudential report relied on information provided in pertinent part by J&J.

24. Among other things, the Prudential report stated:

> JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as . . . GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.

* * *

> If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated . . . stent. . . . According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

25. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Prudential analysts.

26. On January 23, 2006, A.G. Edwards & Sons, Inc. published a report titled "Healthcare Industry Note: The Game May Be Far From Over," attached as Exhibit E ("the AG Edwards report").

27. On information and belief, the AG Edwards report relied on information provided in pertinent part by J&J.

28. Among other things, the AG Edwards report stated:

> We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over.

* * *

> We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a

compound on a stent. We were only given two patent numbers (6776796 [the Falotico '796 patent] and 6585764 [the Wright '764 patent]) . . . .

29. On information and belief, the third patent referenced in J&J's threatening statements was the Wright '536 patent.

30. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to AG Edwards analysts.

31. On January 23, 2006, the International Herald Tribune published an article headlined "J&J works to discredit rival offer for Guidant," attached as Exhibit F ("the International Herald article").

32. On information and belief, the International Herald article relied on information provided in pertinent part by J&J.

33. Among other things, the International Herald article stated:

"J&J is communicating to the Street that Boston Scientific's $80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday.

* * *

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans.

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

> Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.
>
> * * *
>
> Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.
>
> * * *
>
> The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" . . . Guidant's everolimus, he wrote.

34. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to analysts and others.

35. On information and belief, J&J made additional threatening statements to industry analysts, asserting that J&J could prevent Abbott from making or selling the XIENCE V by suing for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. On information and belief, J&J anticipated and intended that Abbott and others would become aware of these threatening statements.

36. On information and belief, J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of the XIENCE V, asserting that the

XIENCE V allegedly infringes the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

37. In March 2006, Guidant publicly announced that the XIENCE V launch would be delayed due to an issue related to manufacturing.

38. As of the date of this Complaint, the XIENCE V launch is imminent. On information and belief, J&J is aware that the XIENCE V launch is imminent and is preparing to sue Abbott for infringement by the XIENCE V of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

39. On information and belief, J&J has never withdrawn or retracted any of its threatening statements that, following the launch of the XIENCE V, J&J would sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

J&J's Assertions In The Patent Office Of Infringement By XIENCE V

40. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 ("Wright '385 application"). The Wright '385 application is related to the Wright '764 patent and the Wright '536 patent. A copy of the Wright Petition is attached as Exhibit G.

41. In the Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '385 application as a patent. Among other things, counsel for J&J asserted:

> Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

42. The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent.

43. On information and belief, J&J is preparing to assert one or more patents in the Wright family, including at least the Wright '764 patent and the Wright '536 patent, against the XIENCE V following its imminent launch.

44. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/829,074 ("Falotico '074 application"). The Falotico '074 application is related to the Falotico '796 patent. A copy of the Falotico Petition is attached as Exhibit H.

45. In the Falotico Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Falotico '074 application as a patent. Among other things, counsel for J&J asserted:

Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

46. The subject matter of at least claim 15 of the Falotico '074 application overlaps with subject matter claimed in the Falotico '796 patent.

47. On information and belief, J&J is preparing to assert one or more patents in the Falotico family, including at least the Falotico '796 patent, against the XIENCE V following its imminent launch.

J&J Has Recently Sued Abbott In An Attempt To Interfere With The XIENCE V Launch

48. On September 25, 2006, J&J filed a complaint in the District Court for the Southern District of New York. Among other things, J&J alleges that Abbott Laboratories tortiously interfered with J&J's intended acquisition of Guidant. The complaint seeks no less than $5.5 billion in damages. A copy of the complaint is attached as Exhibit I.

49. Although the events cited in the complaint occurred over eight months ago, J&J timed the lawsuit, on information and belief, in anticipation of the imminent launch of XIENCE V. Both the timing of the lawsuit and the amount of the damages claimed manifest J&J's intent to cast a cloud over Abbott and interfere with the imminent launch of the XIENCE V.

The XIENCE V Launch Is Imminent

50. As of the date of this Complaint, Abbott will have manufactured, at its facilities in the United States, thousands of XIENCE V products to support its imminent launch.

51. Abbott will continue to manufacture XIENCE V at its facilities in the United States following the launch.

52. Abbott has a reasonable apprehension that J&J intends to sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and Falotico '796 patent by XIENCE V following its imminent launch.

CLAIM I

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,585,764

53. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-52.

54. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '764 patent by XIENCE V.

55. On information and belief, the claims of the Wright '764 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

56. The XIENCE V does not infringe any valid claim of the Wright '764 patent.

57. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '764 patent.

CLAIM II

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,808,536

58. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-57.

59. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '536 patent by XIENCE V.

60. On information and belief, the claims of the Wright '536 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

61. The XIENCE V does not infringe any valid claim of the Wright '536 patent.

62. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '536 patent.

CLAIM III

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,776,796

63. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-62.

64. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Falotico '796 patent by XIENCE V.

65. On information and belief, the claims of the Falotico '796 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

66. The XIENCE V does not infringe any valid claim of the Falotico '796 patent.

67. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Falotico '796 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request entry of judgment in their favor that:

(a) each and every claim of U.S. Patent No. 6,585,764 is invalid;

(b) each and every claim of U.S. Patent No. 6,808,536 is invalid;

(c) each and every claim of U.S. Patent No. 6,776,796 is invalid;

(d) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,585,764;

(e) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,808,536;

(f) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,776,796;

(g) Defendants and their officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, be enjoined from threatening or charging infringement of, or instituting any action for infringement of any of U.S. Patent Nos. 6,585,764, 6,808,536, and 6,776,796 against Plaintiffs, their suppliers, customers, distributors or users of their products;

(h) Defendants pay to Plaintiffs the costs and reasonable attorneys fees incurred by Plaintiffs in this action; and

(i) Plaintiffs be granted such other and further relief as this Court deems just and proper.

JURY TRIAL DEMANDED

Plaintiffs demand a trial by jury on all issues so triable.

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Date: September 29, 2006

EXHIBIT A

US006585764B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 6,585,764 B2**
(45) **Date of Patent: Jul. 1, 2003**

(54) **STENT WITH THERAPEUTICALLY ACTIVE DOSAGE OF RAPAMYCIN COATED THEREON**

(75) Inventors: **Carol Wright**, Somerset, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US); **Ronald Rakos**, Middlesex County, NJ (US); **Kristen King**, Hoboken, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U S C 154(b) by 0 days

(21) Appl No : **09/874,117**

(22) Filed: **Jun. 4, 2001**

(65) **Prior Publication Data**

US 2001/0027340 A1 Oct 4, 2001

Related U.S. Application Data

(63) Continuation of application No. 09/061,568, filed on Apr 16, 1998, now Pat No 6,273,913

(60) Provisional application No 60/044,692, filed on Apr 18, 1997

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** . . **623/1.42**

(58) **Field of Search** 623/1 15, 1.39, 623/1 42, 1 4; 427/2 1–2 31

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Primary Examiner—David H Willse
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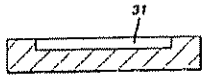
(74) *Attorney, Agent, or Firm*—Paul A Coletti

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis This invention also facilitates the performance of the stent in inhibiting restenosis

20 Claims, 2 Drawing Sheets



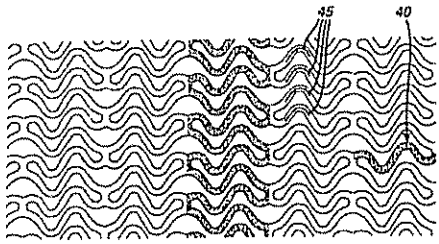


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FIG. 1

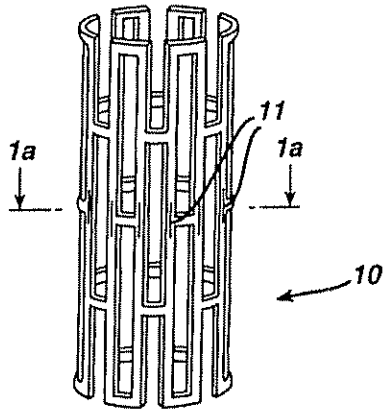


FIG. 1a

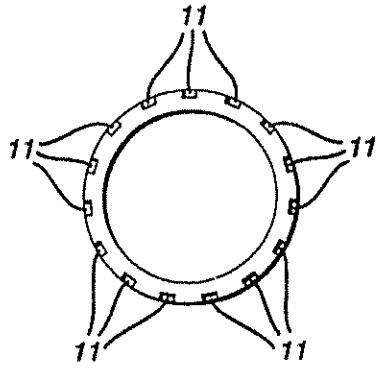


FIG. 2a

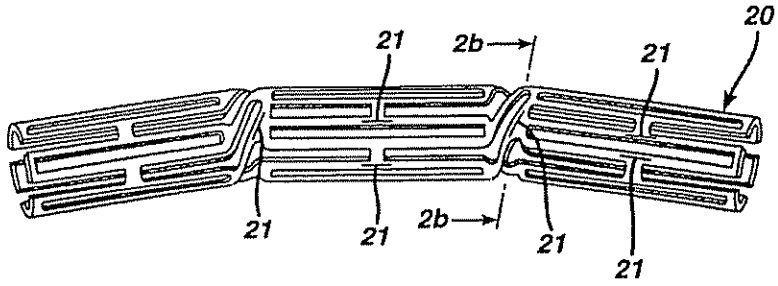


FIG. 2b

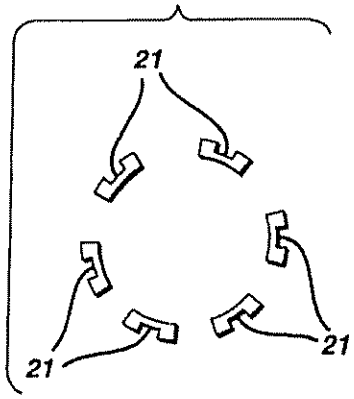


FIG. 3a

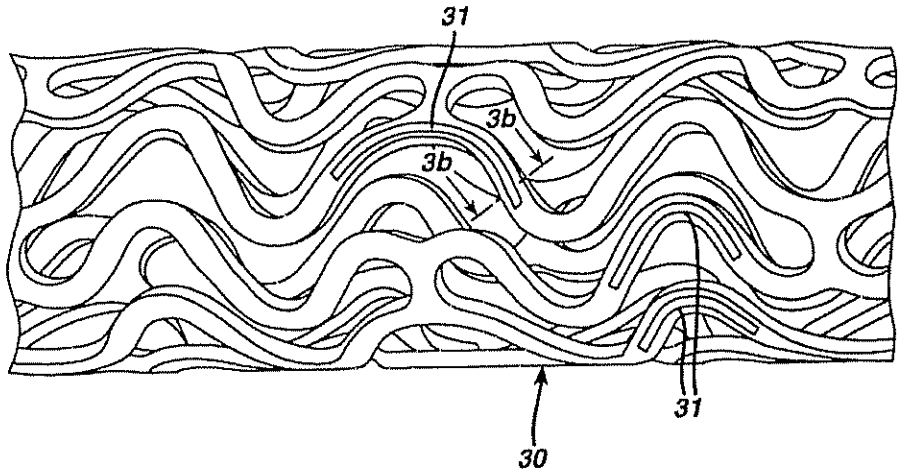


FIG. 3b

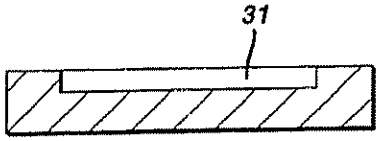
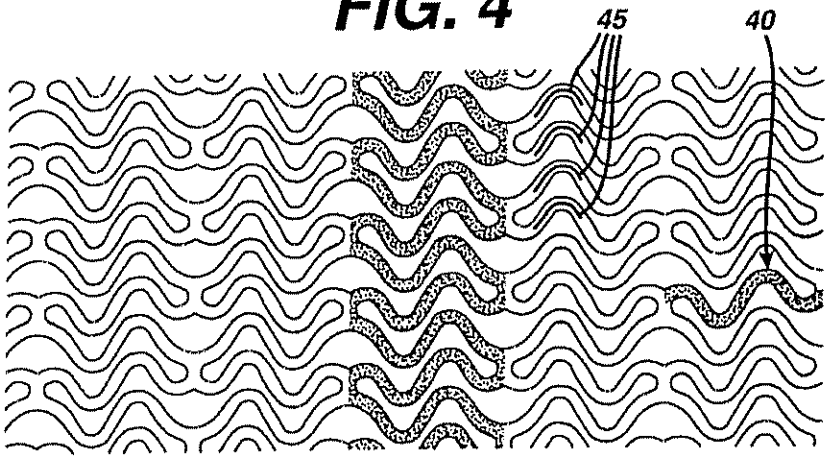


FIG. 4



STENT WITH THERAPEUTICALLY ACTIVE DOSAGE OF RAPAMYCIN COATED THEREON

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U S application Ser No 09/061,568, filed Apr. 16. 1998. now issued as U S Pat No 6,273.913, which claims the benefit of U S Provisional Application No 60/044,692, filed Apr 18, 1997

FIELD OF THE INVENTION

Delivery of rapamycin locally. particularly from an intravascular stent. directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis This invention also facilitates the performance of the stent in inhibiting restenosis

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC) In response to this injury, adhering platelets. infiltrating macrophages, leukocytes. or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima Further proliferation and hyperplasia of intimal SMC and, most significantly. production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow

Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF)

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporir A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF

directly in the etiology of restenosis Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty. the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500. 000–600,000 deaths in the United States annually To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised. direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG)

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery It is currently performed in approximately 250.000–300.000 patients each year The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis)

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus Recently. intravascular stents have been examined as a means of preventing acute reclosure after PTCA

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty While the exact mechanism for restenosis is still under active investigation. the general aspects of the restenosis process have been identified

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref) SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus Endoplasmic reticulum. golgi bodies. and free ribosomes are few and located in the perinuclear region Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF). epidermal growth factor (EGF). etc released from platelets (i e . PDGF) adhering to the damaged arterial luminal surface. invading macrophages and/or leukocytes, or directly from SMC (i e . BFGF) provoke a proliferation and migratory response in medial SMC These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum. golgi and free ribosomes Proliferation/migration usually begins within 1–2 days post-

injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture,* Campbell, J H and Campbell, G R, Eds. CRC Press. Boca Ration, 1987. pp. 39–55); Clowes, A W and Schwartz, S M, Circ Res 56:139–145, 1985)

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response (Liu et al., Circulation, 79:1374–1387. 1989)

Patients with symptomatic reocclusion require either repeat PTCA or CABG Because 30–50% of patients undergoing PTCA will experience restenosis. restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal. attaching a covering or membrane. or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks. and be as thin as possible so as to minimize the increase in profile In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc). To date. the ideal coating material has not been developed for this application

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug The size, shape, position. and number of reservoirs can be used to control the amount of drug. and therefore the dose delivered

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS 1 and 1*a* are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS 2*a* and 2*b* are similar views of an alternate embodiment of the stent with open ends;

FIGS 3*a* and 3*b* are further alternate figures of a device containing a grooved reservoir; and

FIG. 4 is a layout view of a device containing a reservoir as in FIG 3

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty The calcium antagonists have also been unsuccessful in preventing restenosis. although they are still under study Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann Rev Med. 127–132 (1991); Popma et al., 84 *Circulation.* 1426–1436 (1991))

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists. cholesterol lowering agents. and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S M and Faxon, D P, 4 Coronary Artery Disease, 232–242 (1993); Serruys, P W et al., 88 *Circulation,* (part 1) 1588–1601. (1993)

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis Stents, such as the stent **40**, seen in layout in FIG **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery. provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour Med, 495, (1994); Fischman et al., 331 New Eng Jour Med 496–501 (1994) Additionally, in a preliminary trial. heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422 (1996) Thus. 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local. injured tissue off the surface of the stent

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some

activity in experimental animal models These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature,* 25–626, (1977); Guyton, J. R. et al 46 Circ. Res , 625–634, (1980); Clowes, A. W and Clowes, M M . 52 Lab Invest , 611–616, (1985) A W and Clowes, M M., 58 Circ Res , 839–845 (1986); Majesky et al , 61 Circ Res., 296–300, (1987); Snow et al , 137 Am J Pathol., 313–330 (1990); Okada, T. et al , 25 *Neurosurgery,* 92–898. (1989) colchicine (Currier, J W et al , 80 *Circulation,* 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell. J S et al . 245 Science. 186–188 (1989), angiopeptin (Lundergan. C. F et al . 17 Am J Cardiol (Suppl B); 132B–136B (1991), Cyclosporin A (Jonasson. L. et. al . 85 Proc Natl. Acad Sci . 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G A A , et al , 253 *Science,* 1129–1132 (1991), terbinafine (Nemecek, G M et al , 248 J Pharmacol Exp Thera., 1167–11747 (1989), trapidil (Liu. M W et al , 81 *Circulation,* 1089–1093 (1990), interferon-gamma (Hansson, G K and Holm. 84 *J Circulation,* 1266–1272 (1991), steroids (Colburn, M. D. et al . 15 J. Vasc Surg.. 510–518 (1992), see also Berk. B C et al , 17 J Am Coll Cardiol . 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref). and rapamycin (see below)

Of particular interest in rapamycin Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol Res 13: 110–116. 1994) The antiproliferative action of rapamycin is not limited to T-cells; Marx et al (Circ Res 76:412–417. 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al have shown the rat, porcine, and human SMC migrating can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996) Thus. rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al , Transplantation 55:1409–1418, 1993; Gallo et al . in press. (1997)) These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis

Although the ideal agent for restenosis has not yet been identified. some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury. including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent. from a stent graft. grafts, stent cover or sheath

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e g vapour deposition methods such as rf-plasma polymerization) and combinations thereof

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure

1 Experimental Stent Delivery Method—Delivery from Polymer Matrix

Solution of Rapamycin. prepared in a solvent miscible with polymer carrier solution. is mixed with solution of polymer at final concentration range 0 001 weight % to 30 weight % of drug Polymers are biocompatible (i e , not elicit any negative tissue reaction or promote mural thrombus formation) and degradable. such as lactone-based polyesters or copolyesters. e g . polylactide. polycaprolactonglycolide,polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, e g , PEO-PLLA, or blends thereof Nonabsorbable biocompatible polymers are also suitable candidates Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e g , poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof. and the solvent allowed to evaporate to leave a film with entrapped rapamycin

2 Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin. range 0 001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores (The dipping solution can also be compressed to improve the loading efficiency) After solvent has been allowed to evaporate. the stent is dipped briefly in fresh solvent to remove excess surface bound drug A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above This outerlayer of polymer will act as diffusion-controller for release of drug

3 Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization Covalent bonds such as ester, amides or anhydrides may be suitable for this

4 Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e g , polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10*μ* to 1000*μ* The resulting sheet can be wrapped perivascularly on the target vessel Preference would be for the absorbable polymer

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C . range 40°–45° C Mixture is applied in a molten state to the external side of the target vessel Upon cooling to body temperature the mixture solidifies conformally to the vessel wall Both non-degradable and absorbable biocompatible polymers are suitable

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin As seen in FIGS **1***a*, **2***a* and **3***a*, any stent strut **10**. **20**. **30** can be modified to have a certain reservoir or channel **11**. **21**, **31** Each of these reservoirs can be open or closed as desired These reservoirs can hold the drug to be delivered FIG **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent Accordingly, this concept can be useful for "second generation" type stents

In any of the foregoing devices. however. it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area In this regard. the reservoir size in the stent struts must be kept at a size of about 0 0005" to about 0 003" Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount

These and other concepts will are disclosed herein It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents

What is claimed is:

1 A stent having a coating containing rapamycin. said coating formed from a polymer mixed carrier containing the rapamycin; and said coating applied to said stent

2 The stent of claim **1** wherein the stent is dip-coated

3 The stent of claim **1** wherein the stent is sprayed with said coating

4 A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%

5 The stent of claim **4** wherein a polymer is mixed to the rapamycin or its analogs

6 The stent of claim **4** wherein a polymer is bound to the rapamycin or its analogs

7 The stent of claim **4** wherein the rapamycin or its analogs is entrapped on the surface of the stent by a polymer

8 A stent having a coating containing rapamycin. said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is biocompatible and degradable; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers

9 A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers.

10 A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is nonabsorbable; and

wherein the polymer is chosen from: polydimethylsiolxane; poly(ethylene)vinylacetate; poly(hydroxy) ethylmethylmethacrylate. polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters

11 A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: polydimethylsiolxane; poly(ethylene)vinylacetate; poly(hydroxy) ethylmethylmethacrylate. polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters

12 A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said applied to said strut. and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin coating applied therein

13 A stent having a coating containing rapamycin or its analogs. wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%, wherein the coating is a polymer.

14 The stent of claim **13** wherein said polymer is mixed to the rapamycin or its analogs

15 The stent of claim **4** wherein said polymer is bound to the rapamycin or its analogs

16 The stent of claim **13** wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer

17 A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis

18 The stent of claim **17** wherein said polymer is mixed to the rapamycin or its analogs

19 The stent of claim **17** wherein said polymer is bound to the rapamycin or its analogs

20 The stent of claim **17** wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer

* * * * *

EXHIBIT B

US006808536B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 6,808,536 B2**
(45) **Date of Patent: *Oct. 26, 2004**

(54) **STENT CONTAINING RAPAMYCIN OR ITS ANALOGS USING A MODIFIED STENT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U S C 154(b) by 0 days

This patent is subject to a terminal disclaimer

(21) Appl No : **10/408,328**

(22) Filed: **Apr. 7, 2003**

(65) **Prior Publication Data**

US 2003/0176915 A1 Sep. 18, 2003

Related U.S. Application Data

(63) Continuation of application No 09/874,117, filed on Jun 4, 2001, now Pat No. 6,585,764 which is a continuation of application No 09/061,568, filed on Apr 16, 1998, now Pat No 6,273,913

(60) Provisional application No 60/044,692 filed on Apr 18, 1997

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Search** . . 623/1 15, 1 39, 623/1 42. 1 4; 427/2 1–2 31

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Primary Examiner—Suzette J Jackson

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis This invention also facilitates the performance of the stent in inhibiting restenosis

6 Claims, 2 Drawing Sheets

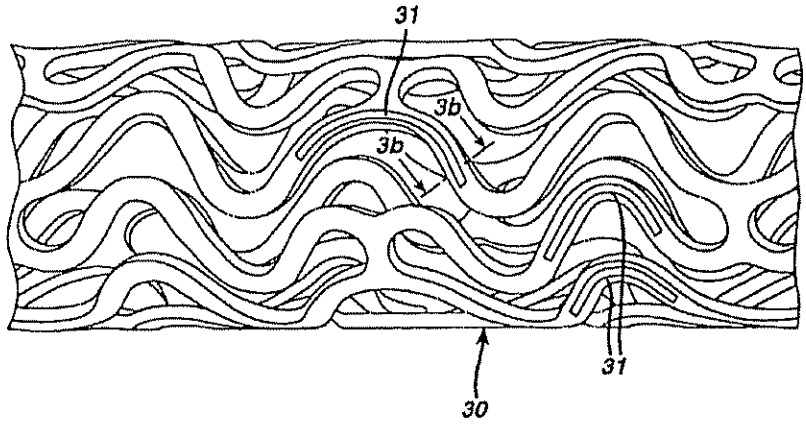

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FIG. 1

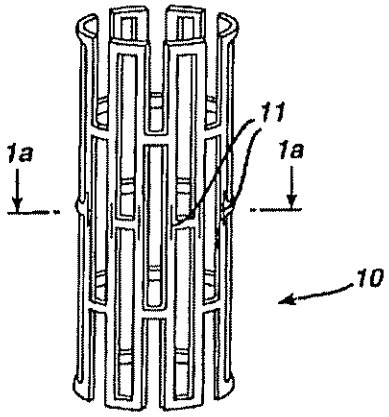


FIG. 1a

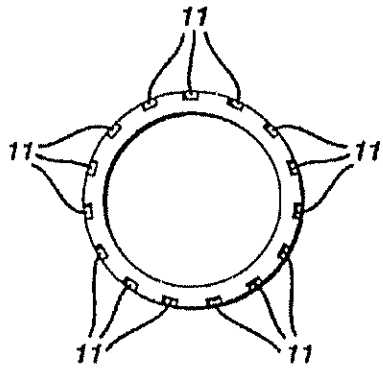


FIG. 2a

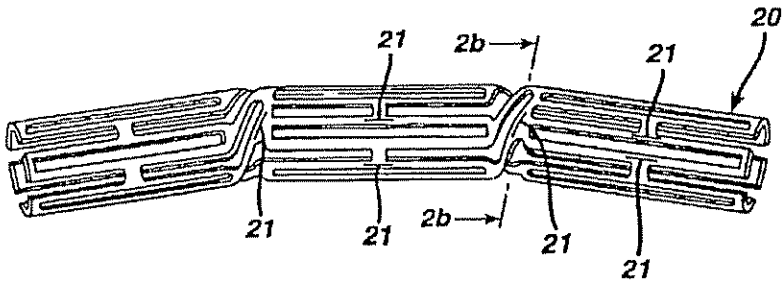


FIG. 2b

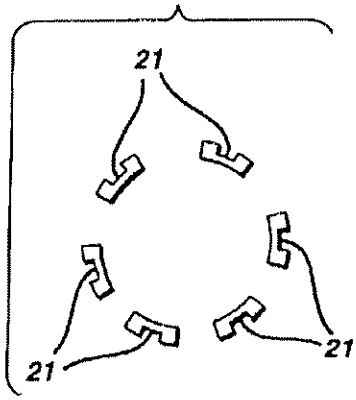


FIG. 3a

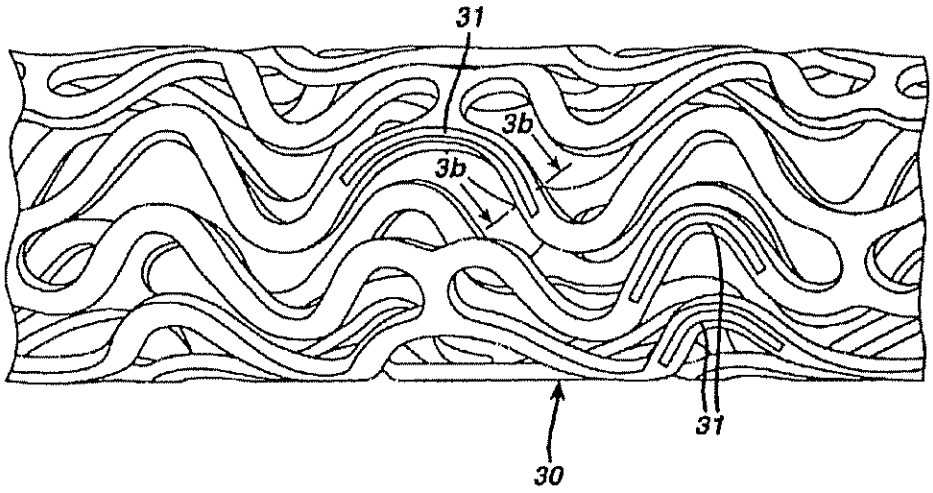


FIG. 3b

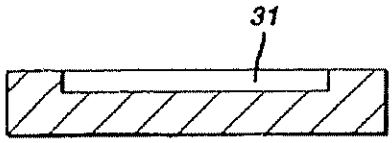
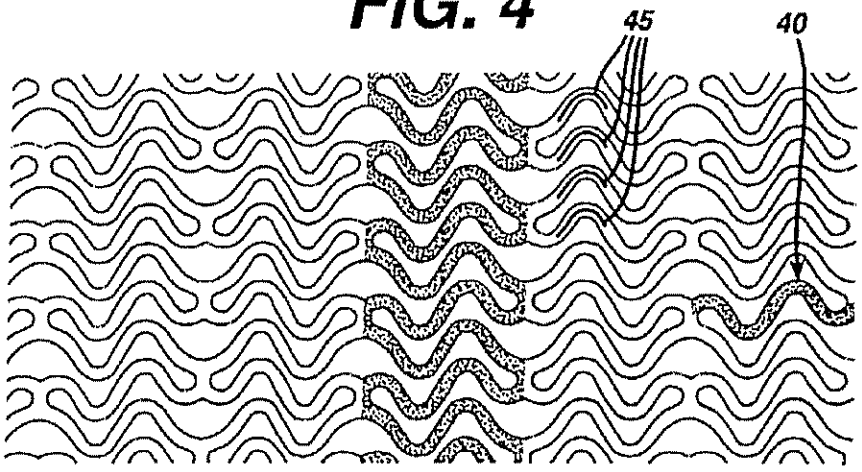


FIG. 4



STENT CONTAINING RAPAMYCIN OR ITS ANALOGS USING A MODIFIED STENT

Continuation of prior application Ser No: 09/874,117, filed Jun 4, 2001, now U S Pat No 6,585,764 which is a continuation of Ser. No 09/061,568 filed Apr. 16, 1998, now U S Pat No 6,273,913; which claim the benefit of U.S. Provisional Application No 60/044,692, filed Apr 18, 1997

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent. directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent. to inhibit neointimal tissue proliferation and thereby prevent restenosis This invention also facilitates the performance of the stent in inhibiting restenosis

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery. also injures resident coronary arterial smooth muscle cells (SMC) In response to this injury. adhering platelets, infiltrating macrophages. leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow

Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF)

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers. angiotensin converting enzyme inhibitors (captopril. cilazapril), cyclosporin A, trapidil (an antianginal. antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives). and c-myc and c-myb antinsense oligonucleotides

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world Most coronary artery-related deaths are due to atherosclerosis Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG)

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery It is currently performed in approximately 250,000–300,000 patients each year The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis)

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus Recently. intravascular stents have been examined as a means of preventing acute reclosure after PTCA

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified:

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0 1%/day; ref) SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus Endoplasmic reticulum. golgi bodies. and free ribosomes are few and located in the perinuclear region Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state

Upon pressure expansion of an intracoronary balloon catheter during angioplasty. smooth muscle cells within the arterial wall become injured Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc released from platelets (i e , PDGF) adhering to the damaged arterial luminal surface. invading macrophages and/or leukocytes. or directly from SMC (i e . BFGF) provoke a proliferation and migratory response in medial SMC These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum. golgi and free ribosomes Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media. rapidly declining thereafter (Campbell et al , In: *Vascular Smooth Muscle Cells in Culture*, Campbell, J. H and Campbell, G R , Eds, CRC Press, Boca Ration, 1987, pp 39–55); Clowes, A W and Schwartz, S M , Circ Res 56:139–145. 1985)

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response (Liu et al , Circulation, 79:1374–1387. 1989)

Patients with symptomatic reocclusion require either repeat PTCA or CABG Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to, coronary artery disease Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury. prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal. attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile In addition. the coating material should not contribute to any adverse response by the body (i e , should be non-thrombogenic, non-inflammatory, etc). To date, the ideal coating material has not been developed for this application

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug The size, shape. position. and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS 1 and 1A are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS 2*a* and 2*b* are similar views of an alternate embodiment of the stent with open ends;

FIGS 3*a* and 3*b* are further alternate figures of a device containing a grooved reservoir; and

FIG. 4 is a layout view of a device containing a reservoir as in FIG 3

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study Other agents currently under study include thromboxane inhibitors. prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al , 42 Ann Rev Med . 127–132 (1991); Popma et al , 84 *Circulation,* 1426–1436 (1991))

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements. thromboxane receptor antagonists. cholesterol lowering agents. and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin. S M and Faxon. D P., 4 Coronary Artery Disease, 232–242 (1993); Serruys, P W et al , 88 *Circulation*, (part 1) 1588–1601, (1993)

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis Stents. such as the stent **10** seen in layout in FIG 4. balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery. provide structural support to the arterial wall This support is helpful in maintaining an open path for blood flow In two randomized clinical trials. stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al , 331 New Eng Jour Med. 495, (1994); Fischman et al , 331 New Eng Jour Med, 496–501 (1994) Additionally, in a preliminary trial. heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al . 93 Circulation. 412–422. (1996) Thus. 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention. and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J R et al 46 Circ Res , 625–634, (1980); Clowes, A W and Clowes. M M , 52 Lab

Invest . 611–616, (1985); Clowes, A W and Clowes. M M , 58 Circ. Res., 839–845 (1986); Majesky et al , 61 Circ Res., 296–300, (1987); Snow et al , 137 Am J Pathol., 313–330 (1990); Okada, T et al , 25 *Neurosurgery*, 92–898, (1989) colchicine (Currier. J W et al . 80 *Circulation*, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J S et al , 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F et al , 17 Am J Cardiol (Suppl B); 132B–136B (1991), Cyclosporin A (Jonasson, L. et. al , 85 Proc Nati, Acad Sci , 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G A A , et al . 253 Science, 1129–1132 (1991). terbinaline (Nemecek, G M et al , 248 J Pharmacol Exp Thera . 1167–11747 (1989), trapidil (Liu. M W et al . 81 *Circulation*. 1089–1093 (1990). interferon-gamma (Hansson, G K and Holm. 84 J Circulation. 1266–1272 (1991), steroids (Colburn, M. D et al . 15 J. Vasc Surg , 510–518 (1992), see also Berk. B C et al . 17 J Am Coll Cardiol . 111B–117B (1991). ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref). gene vectors (ref), and rapamycin (see below)

Of particular interest in rapamycin Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka. Immunol Res 13: 110–116, 1994) The antiproliferative action of rapamycin is not limited to T-cells; Marx et al (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al have shown the rat. porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996) Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response In fact. the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al , Transplantation 55:1409–1418. 1993; Gallo et al . in press, (1997)) These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent. from a stent graft, grafts, stent cover or sheath

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e g vapour deposition methods such as rf-plasma polymerization) and combinations thereof

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure

1 Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0 001 weight % to 30 weight % of drug Polymers are biocompatible (i e . not elicit any negative tissue reaction or promote mural thrombus formation) and degradable. such as lactone-based polyesters or copolyesters. e g . polylactide. polycaprolactonglycolide, polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, e g . PEO-PLLA. or blends thereof Nonabsorbable biocompatible polymers are also suitable candidates Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e g , poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating. or spray coating, or brush coating or dip/spin coating or combinations thereof. and the solvent allowed to evaporate to leave a film with entrapped rapamycin

2 Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0 001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores (The dipping solution can also be compressed to improve the loading efficiency) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above This outerlayer of polymer will act as diffusion-controller for release of drug

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization Covalent bonds such as ester. amides or anhydrides may be suitable for this

4 Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted. with a degradable

polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e g . polydimethylsiloxane, and mixture cast as a thin sheet. thickness range 10μ to 1000μ The resulting sheet can be wrapped perivascularly on the target vessel Preference would be for the absorbable polymer

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C . range 40°–45° C Mixture is applied in a molten state to the external side of the target vessel Upon cooling to body temperature the mixture solidifies conformally to the vessel wall Both non-degradable and absorbable biocompatible polymers are suitable

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin As seen in FIGS **1***a*. **2***a* and **3***a*, any stent strut **10**. **20**. **30** can be modified to have a certain reservoir or channel **11**. **21**. **31** Each of these reservoirs can be open or closed as desired These reservoirs can hold the drug to be delivered FIG **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut Of course. this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent Accordingly, this concept can be useful for "second generation" type stents

In any of the foregoing devices. however. it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area In this regard, the reservoir size in the stent struts must be kept at a size of about 0 0005" to about 0 003" Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount

These and other concepts will are disclosed herein It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however. the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents

What is claimed is:

1 A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%. said stent further comprising:

a generally thin walled cylinder. said cylinder containing a plurality of generally solid struts. said coating applied to said strut. and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top. and said channel smaller in all dimensions than said strut. said channel containing a reservoir of said rapamycin containing coating applied therein

2 A stent having a coating containing rapamycin or its analogs. wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%, wherein the coating is a polymers said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top. and said channel smaller in all dimensions than said strut. said channel containing a reservoir of said rapamycin containing coating applied therein

3 A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis. said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts. said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top. and said channel smaller in all dimensions than said strut. said channel containing a reservoir of said rapamycin containing coating applied therein

4 A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%. said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts

5 A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0 0001% to 30%, wherein the coating is a polymer. said stent further comprising:

a generally thin walled cylinder. said cylinder containing a plurality of generally solid struts. said coating applied to said struts

6 A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis. said stent further comprising:

a generally thin walled cylinder. said cylinder containing a plurality of generally solid struts. said coating applied to said struts

* * * * *

EXHIBIT C

US006776796B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 6,776,796 B2**
(45) **Date of Patent: Aug. 17, 2004**

(54) **ANTIINFLAMMATORY DRUG AND DELIVERY DEVICE**

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(73) Assignee: **Cordis Corportation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U S C 154(b) by 129 days

(21) Appl No : **09/850,232**

(22) Filed: **May 7, 2001**

(65) **Prior Publication Data**

US 2002/0016625 A1 Feb 7, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No 09/575,480, filed on May 19, 2000

(60) Provisional application No 60/263,979, filed on Jan 25, 2001, provisional application No 60/263,806, filed on Jan 24, 2001, provisional application No 60/262,614, filed on Jan 18, 2001, provisional application No 60/262,461, filed on Jan. 18, 2001 and provisional application No 60/204,417, filed on May 12, 2000

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.46**

(58) **Field of Search** 623/1 42, 1 43, 623/1 44, 1 45, 1 46

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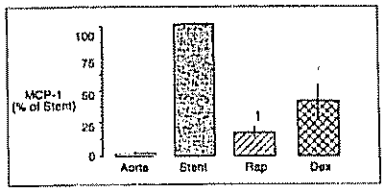
(57) **ABSTRACT**

A drug and drug delivery system may be utilized in the treatment of vascular disease A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity

11 Claims, 2 Drawing Sheets



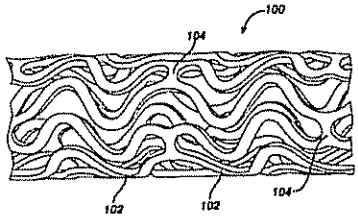


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FIG. 1

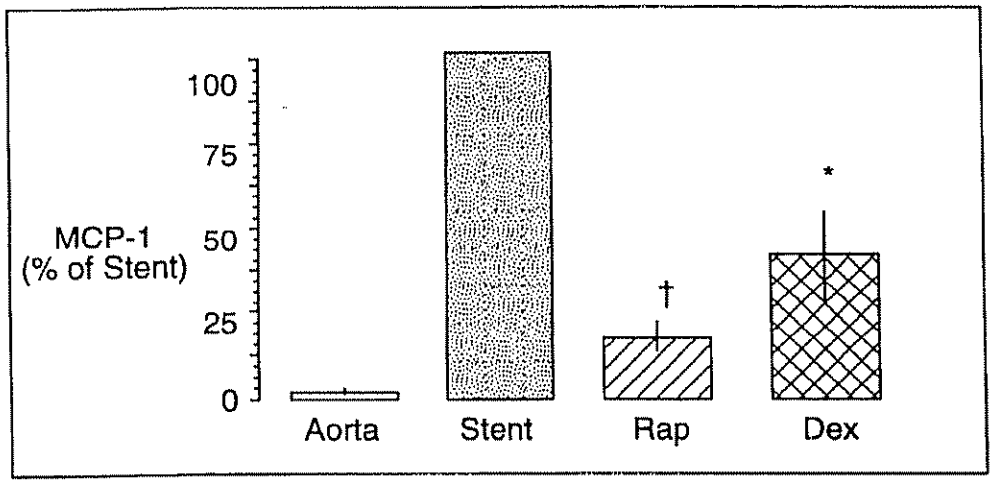


FIG. 2

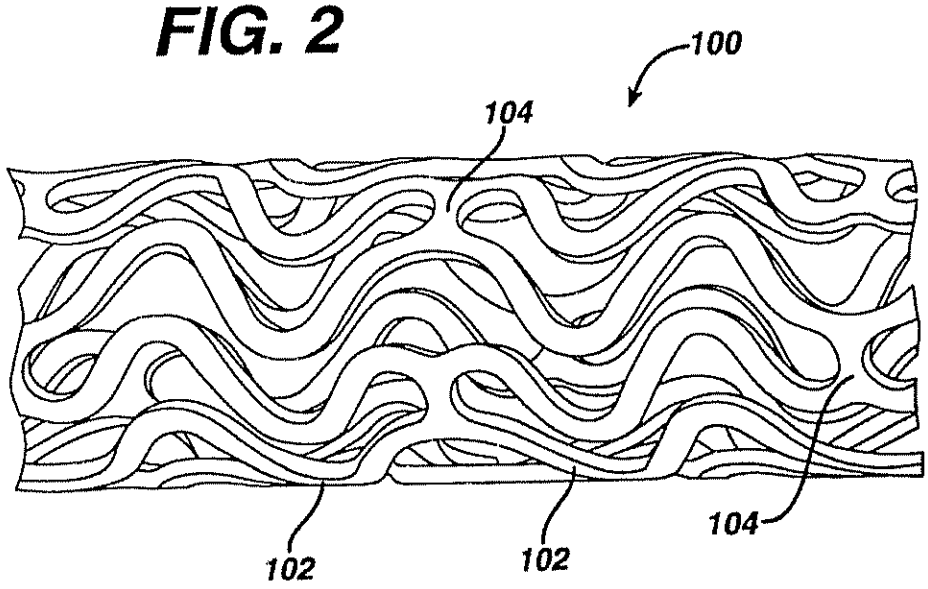
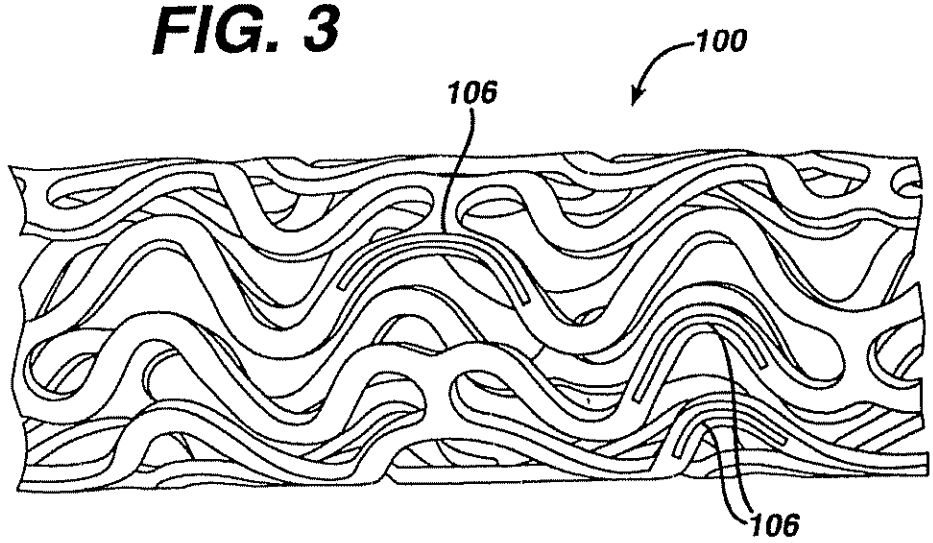


FIG. 3



ANTIINFLAMMATORY DRUG AND DELIVERY DEVICE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S application Ser No 09/575,480, filed on May 19, 2000 which claims the benefit of U S Provisional Application No 60/204,417, filed May 12, 2000 and claims the benefit of. U.S Provisional Application No 60/262,614, filed Jan 18, 2001. U S Provisional Application No 60/262,461, filed Jan 18, 2001, U.S Provisional Application No 60/263,806, filed Jan 24, 2001 and U S Provisional Application No 60/263,979, filed Jan 25, 2001

BACKGROUND OF THE INVENTION

1 Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia

2 Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients More severe blockage of blood vessels in such individuals often leads to hypertension. ischemic injury. stroke, or myocardial infarction Atherosclerotic lesions, which limit or obstruct coronary blood flow. are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure Additionally. restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury Multiple processes. including thrombosis, inflammation, growth factor and cytokine release, cell proliferation. cell migration and extracellular matrix synthesis each contribute to the restenotic process

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified In the normal arterial wall. smooth muscle cells proliferate at a low rate. approximately less than 0 1 percent per day Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell. 1985)

Upon pressure expansion of an intracoronary balloon catheter during angioplasty. smooth muscle cells within the vessel wall become injured. initiating a thrombotic and inflammatory response Cell derived growth factors such as platelet derived growth factor. fibroblast growth factor. epidermal growth factor. thrombin, etc , released from platelets, invading macrophages and/or leukocytes. or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum. Golgi and free ribosomes Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell. 1987; Clowes and Schwartz. 1985)

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima. usually within seven to fourteen days post-injury The newly formed tissue is called neointima The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury Within three to seven days post-injury. inflammatory cells have migrated to the deeper layers of the vessel wall In animal models employing either balloon injury or stent implantation. inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al , 1993; Edelman et al , 1998) Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A W and Karnovsky M , Nature 265: 25–26, 1977; Guyton, J R et al . Circ Res , 46: 625–634, 1980; Clowes, A W and Clowes. M M . Lab Invest 52: 611–616, 1985; Clowes. A W and Clowes, M M . Circ Res 58: 839–845. 1986; Majesky et al . Circ Res 61: 296–300. 1987; Snow et al . Am J Pathol 137: 313–330, 1990; Okada, T et al , Neurosurgery 25: 92–98, 1989). colchicine (Currier, J W et al , Circ 80: 11–66, 1989). taxol (Sollot. S J et al , J Clin Invest 95: 1869–1876, 1995). angiotensin converting enzyme (ACE) inhibitors (Powell, J S et al , Science. 245: 186–188, 1989). angiopeptin (Lundergan, C F et al Am J Cardiol 17(Suppl B):132B-136B, 1991), cyclosporin A (Jonasson, L et al., Proc Natl . Acad Sci , 85: 2303, 1988). goat-anti-rabbit PDGF antibody (Ferns. G A A . et al , Science 253: 1129–1132. 1991). terbinafine (Nemecek, G M et al , J Pharmacol. Exp Thera 248: 1167–1174. 1989). trapidil (Liu. M W et al . Circ 81: 1089–1093. 1990), tranilast (Fukuyama, T et al . Eur. J Pharmacol 318: 327–332. 1996), interferon-gamma (Hansson. G K and Holm. J. Circ 84:1266–1272, 1991). rapamycin (Marx, S O et al.. Circ Res 76: 412417. 1995), corticosteroids (Colburn. M D et al , J Vasc Surg 15: 510–518, 1992), see also Berk. B C et al , J Am. Coll. Cardiol 17: 111 B-117B, 1991), ionizing radiation (Weinberger, J et al , Int J Rad Onc Biol Phys 36: 767–775, 1996), fusion toxins (Farb. A et al .

Circ Res 80: 542–550, 1997) antisense oligonucleotides (Simons, M et al, Nature 359: 67–70, 1992) and gene vectors (Chang, M W. et al., J Clin Invest 96: 2260–2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al, 1991; Popma et al, 1991) The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al, 1991; Popma et al, 1991)

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993; Serruys, P W. et al, 1993) Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al, 1997; Yokoi, et al, 1997) Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al, 1997) Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall This support is helpful in maintaining vessel lumen patency In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al, 1994; Fischman et al, 1994)

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al, 1996) Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above

In accordance with one aspect, the present invention is directed to a method for the treatment of intimal hyperplasia in vessel walls The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts

In accordance with another aspect, the present invention is directed to a drug delivery device The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of inflammation caused by injury

In accordance with another aspect, the present invention is directed to a method for the treatment of inflammation in vessel walls The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i e restenosis, following percutaneous transluminal coronary angioplasty and stent implantation It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds Other benefits include reduced systemic toxicity, single treatment, and ease of administration An additional benefit of a local delivery device and drug,

agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings

FIG 1 is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories

FIG 2 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern

FIG 3 is a perspective view of the stent of FIG 1 having reservoirs in accordance with the present invention

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia

Rapamycin is a macrocyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U S Pat No 3,929,992 It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation The operation and various functions of rapamycin are described in detail below Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically This is the basis for its immunosuppresive activity and its ability to prevent graft rejection

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12 The complex of rapamycin and FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS) Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i e proximal and distal Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months Accordingly, these results support the hypothesis that rapamycin reduces remodeling

TABLE 1 0

Angiographic In-Lesion Percent Diameter Stenosis (% mean ± SD and "n=" In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4–6 month Follow Up	12 month Follow Up
Brazil	10 6 ± 8 7 (30)	13.6 ± 8 6 (30)	22 3 ± 7 2 (15)
Netherlands	14 7 ± 8 8	22 4 ± 6 4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35–430 ug/15–18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below

TABLE 3.0

Animal Studies with Rapamycin-coated stents
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	Neointimal Area N (mm^2)	% Change From Polymr	% Change From Metal
Porcine						
98009	14 days	Metal		8 2.04 ± 0.17		
		1X + rapamycin	153 μg	8 1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 μg	8 1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10 2.29 ± 0.21		
				9 3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 μg	8 2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 μg	9 2.62 ± 0.21		+14%
99006	28 days	Metal		12 4.57 ± 0.46		
		EVA/BMA 3X		12 5.02 ± 0.62		+10%
		1X + rapamycin	125 μg	11 2.84 ± 0.31*	-43%	-38%
		3X + rapamycin	430 μg	12 3.06 ± 0.17*	-39%	-33%
		3X + rapamycin	157 μg	12 2.77 ± 0.41*	-45%	-39%
99011	28 days	Metal		11 3.09 ± 0.27		
				11 4.52 ± 0.37		
		1X + rapamycin	189 μg	14 3.05 ± 0.35		-1%
		3X + rapamycin/dex	182/363 μg	14 2.72 ± 0.71		-12%
99021	60 days	Metal		12 2.14 ± 0.25		
		1X + rapamycin	181 μg	12 2.95 ± 0.38		+38%
99034	28 days	Metal		8 5.24 ± 0.58		
		1X + rapamycin	186 μg	8 2.47 ± 0.33*		-53%
		3X + rapamycin/dex	185/369 μg	6 2.42 ± 0.64*		-54%
20001	28 days	Metal		6 1.81 ± 0.09		
		1X + rapamycin	172 μg	5 1.66 ± 0.44		-8%
20007						
	30 days	Metal		9 2.94 ± 0.43		
		1XTC + rapamycin	155 μg	10 1.40 ± 0.11*		-52%*

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm²)	% Change From Polyme	% Change From Metal
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 μg	9	0.92 ± 0.14	-27%	-23%
		1X + rapamycin	196 μg	10	0.66 ± 0.12**	-48%	-45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 μg	8	0.81 ± 0.16		-32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively
TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA;
Biphasic: 2x 1X layers of rapamycin in EVA/BMA separated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3d prior to stent implantation
*p < 0.05 from EVA/BMA control
**p < 0.05 from Metal;
[#]Inflammation score: (0 = essentially no intimal involvement;
1 = <25% intima involved;
2 = ≥25% intima involved;
3 = >50% intima involved)

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm²)	% Change From Polyme	% Change From Metal	Inflammation Score #
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 μg	10	0.29 ± 0.03		-24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		-52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 μg	10	3.03 ± 0.29		-12%	0.80 ± 0.23
		1X + rapamycin	171 μg	10	2.86 ± 0.35		-17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 μg	10	3.34 ± 0.31		-8%	1.50 ± 0.34
		1X + rapamycin	171 μg	10	3.87 ± 0.28		+6%	1.68 ± 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus ITM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	1.8% ± 6.1% (30)	[-2.6%, 7.0%]
Range (min, max)	(-8.2%, 14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 7.6% (13)	[4.8%, 13.0%]
Range (min, max)	(-2.9%, 20.4%)	
12-month In-Stent		

TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Diameter Stenosis (%)		
Mean ± SD (N) Range (min, max) 4-month In-Stent Late Loss (mm)	8.9% ± 6.1% (15) (-3.0%, 22.0%)	[5.8%, 12.0%]
Mean ± SD (N) Range (min, max) 6-month In-Stent Late Loss (mm)	0.00 ± 0.29 (30) (-0.51, 0.45)	[-0.10, 0.10]
Mean ± SD (N) Range (min, max) 12-month In-Stent Late Loss (mm)	0.25 ± 0.27 (13) (-0.51, 0.91)	[0.10, 0.39]
Mean ± SD (N) Range (min, max) 4-month Obstruction Volume (%) (IVUS)	0.11 ± 0.36 (15) (-0.51, 0.82)	[-0.08, 0.29]
Mean ± SD (N) Range (min, max) 6-month Obstruction Volume (%) (IVUS)	10.48% ± 2.78% (28) (4.60%, 16.35%)	[9.45%, 11.51%]
Mean ± SD (N) Range (min, max) 12-month Obstruction Volume (%) (IVUS)	7.22% ± 4.60% (13) (3.82%, 19.88%)	[4.72%, 9.72%].
Mean ± SD (N) Range (min, max) 6-month Target Lesion Revascularization (TLR)	2.11% ± 5.28% (15) (0.00%, 19.89%) 0.0% (0/30)	[0.00%, 4.78%]. [0.0%, 9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%, 18.1%]

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexamethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

*significance level $P < 0.05$

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients

receiving rapamycin delivered locally from a stent The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i e at S, G2 or M phase

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27 Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i e an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12 The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product Wortmanin may be an agent which inhibits the function of this class of proteins It may also be a peptide or an oligonucleotide sequence The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter) For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis Intravascular ultrasound studies (Mintz et al, 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen As set forth below, self-expanding stents may also be utilized

FIG 2 illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open.

more particularly for protecting a segment of artery from restenosis after angioplasty The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts

The stent **100** generally comprises first and second ends with an intermediate section therebetween The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**. wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure Essentially. each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102** The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band

The stent **100** may be fabricated utilizing any number of methods For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling. chemical etching or other means The stent **100** is inserted into the body and placed at the desired site in an unexpanded form In one embodiment. expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium In this embodiment. after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means. wherein the insertion means include a suitable catheter, or flexible rod On emerging from the catheter. the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure. temperature or electrical stimulation

FIG **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG **2** As illustrated, the stent **100** may be modified to comprise a reservoir **106** Each of the reservoirs may be opened or closed as desired These reservoirs **106** may be specifically designed to hold the drug, agent. compound or combinations thereof to be delivered Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area In this regard. the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount

In an alternate exemplary embodiment. the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts A detailed description of exemplary coating techniques is described below

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days

Any number of non-erodible polymers may be utilized in conjunction with rapamycin In the exemplary embodiment. the polymeric matrix comprises two layers The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate The rapamycin is incorporated into this layer The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules Polymers are permeable, thereby allowing solids, liquids and gases to escape therefrom The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways For example. the solution may be sprayed onto the stent or the stent may be dipped into the solution In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry In another exemplary embodiment. the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity In this manner, the solution and stent will be attracted to one another In using this type of spraying process. waste may be reduced and more control over the thickness of the coat may be achieved

Since rapamycin works by entering the surrounding tissue. it is preferably only affixed to the surface of the stent making contact with one tissue Typically. only the outer surface of the stent makes contact with the tissue Accordingly, in a preferred embodiment. only the outer surface of the stent is coated with rapamycin For other drugs. agents or compounds. the entire stent may be coated

It is important to note that different polymers may be utilized for different stents For example. in the above-described embodiment. ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix This matrix works well with stainless steel stents Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium

Although shown and described is what is believed to be the most practical and preferred embodiments. it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims

What is claimed is:

1 A method for the treatment of intimal hyperplasia in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts. the anti-inflammatory agent comprises

analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and possesses the same pharmacologic properties as rapamycin

2 Method for the treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent reduces inflammatory cytokine levels in vascular tissues

3 The method for the treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent reduces monocyte chemotactic protein levels in vascular tissues

4 The method for treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent comprises rapamycin

5 A drug delivery device comprising:

an implantable intraluminal medical device; and

a therapeutic dosage of an agent releasably affixed to the implantable intraluminal medical device for the treatment of inflammation caused by injury, the agent being released for a sustained period of time in the range from about two to about six weeks, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and posses the same pharmacologic properties as rapamycin

6 The drug delivery device according to claim 5, wherein the agent reduces inflammatory cytokine levels in vascular tissue

7 The drug delivery device according to claim 5, wherein the agent reduces monocyte chemotactic protein levels in vascular tissues

8 The drug delivery device according to claim 5, wherein the agent comprises rapamycin

9 The drug delivery device according to claim 5, wherein the intraluminal medical device comprises a stent

10 The drug delivery device according to claim 9, wherein the agent is incorporated in a non-erodible polymeric matrix coating affixed to the stent

11 A method for the treatment of inflammation in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device of an anti-inflammatory agent in therapeutic dosage amounts, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and posses the same pharmacologic properties as rapamycin

* * * * *

EXHIBIT D

January 20, 2006 **Prudential Equity Group, LLC**

Healthcare
Medical Devices

JNJ: TAKES OFF THE GLOVES IN ITS FIGHT WITH BOSTON SCIENTIFIC FOR GUIDANT

Johnson & Johnson

Larry Biegelsen • 212 778 5825 • lawrence_biegelsen@prusec.com
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JNJ | $61.48 | NYSE

Current:	**Underweight**
Risk:	**Low**
Target:	**$59.00**
Industry:	**Favorable**

All important disclosures and Regulation AC disclosure can be found at the end of this report, starting at page 6, under the section entitled Important Disclosures and Regulation AC Disclosure, respectively.

Includes Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	**$47,348.0E**	**$2.99E**	20.6X	$0.80A	$0.79A	$0.75A	$0.64A
Current	**12/05**	**$51,214.0E**	**$3.37E**	**18.2X**	**$0.94A**	**$0.90A**	**$0.85A**	**$0.69E**
Current	**12/06**	**$53,758.0E**	**$3.61E**	**17.0X**	**$1.01E**	**$0.95E**	**$0.89E**	**$0.76E**

Without Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	**$47,348.0E**	$3.10A	19.8X	$0.83A	$0.82A	$0.78A	$0.67A
Current	**12/05**	**$51,214.0E**	**$3.49E**	**17.6X**	**$0.97A**	**$0.93A**	**$0.87A**	**$0.72E**
Current	**12/06**	**$53,758.0E**	**$3.74E**	**16.4X**	**$1.04E**	**$0.98E**	**$0.93E**	**$0.79E**

Avg Volume: **8,700,000**
Market Cap: **$191,808** m
Shares: **3,119.84** m

Div/Yield: **1.32/2.15%**
52w Range: **70.00-59.80**

EPS Growth: **NA**
P/E / Growth: **NM**

HIGHLIGHTS

- As the 1/25 deadline to make a counter-offer for GDT approaches, JNJ is communicating to the Street that BSX's $80/share offer for GDT is fraught with uncertainty which leads us to believe that JNJ is still very interested in acquiring GDT and that JNJ will likely increase its offer at least one more time.
- We believe JNJ will have to raise its offer to about $78/share from $71/share in order to gain the GDT board's approval.
- Although a JNJ offer of $78/share would be 3% below BSX's, there is precedent for a board to accept a lower offer. In 5/05, Verizon acquired MCI for $8.44B or 13% less than what Qwest offered because Verizon was seen as a more stable company.
- JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as ABT's zotarolimus and GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.
- Our analysis indicates that an offer of $78/share for GDT would be slightly more dilutive for JNJ compared to its current $71/share offer but still accretive on a cash basis in '08. In addition, our analysis indicates that JNJ could offer $90/share for GDT before an acquisition of STJ is more attractive.

Healthcare
Medical Devices

DISCUSSION

As the January 25th deadline for JNJ to make a counter-offer for Guidant (GDT-$75.89; Neutral Weight Rated) approaches, JNJ is communicating to the Street that Boston Scientific's (BSX-$23.36; Neutral Weight Rated) $80/share offer for GDT is fraught with uncertainty. This leads us to believe that JNJ is still very much interested in acquiring GDT and that JNJ will likely increase its offer for GDT at least one more time. We believe JNJ will have to increase its offer to at least $78/share from its previous offer of $71/share if it hopes to gain the GDT board's approval. Although a JNJ offer of $78/share would be 3% below BSX's, there is precedent for a board and shareholders to accept a lower offer. In May 2005, Verizon acquired MCI for $8.44 billion or 13% less than what Qwest offered because VZ was seen as a more stable company. During the bidding process, Q forced VZ to raise its offer for MCI from $20.35/share to $26/share. Although the situation with VZ and Q is not a perfect analogy, we could envision a similar scenario playing out with GDT given the lower risk associated with the JNJ offer and the greater liquidity of JNJ shares compared to BSX shares once a deal is completed. Interestingly, BSX's stock price is moving closer to the lower end of the collar ($22.62). If BSX's stock price falls to $22.00, its offer for GDT would become $79/share (see Figure 1 below).

Figure 1: Impact of Collar on BSX's Offer For GDT if BSX's Share Price Reaches $22.00

BSX Current Price:	$23.36
Collar Max:	$28.86
Collar Min:	$22.62
Proposed Cash Component of BSX Offer:	$42.00
Proposed Stock Component of BSX Offer:	$38.00
Proposed Total BSX Offer for GDT:	$80.00
Assumed BSX Stock Price:	**$22.00**
Collared Exchange Ratio:	1.68
Resulting Stock Component of BSX Offer:	$36.96
Resulting Total Value of BSX Offer:	$78.96
Lost Value Per GDT Share:	**-$1.04**
GDT Fully Diluted Shares (mm):	335
Market Value Impact ($mm):	-$349

Source: Company reports, Prudential Equity Group, LLC estimates, Reuters

JNJ's acquisition of GDT has already received regulatory clearance in the U.S. and E.U. In order to receive approval from the FTC, JNJ was forced to license out rapid exchange (RX) stent technology as well as certain JNJ patents which cover the use of rapamycin derivatives such as Novartis's (NVS: $54.98; Overweight rated by Prudential Equity Group's Senior Pharmaceutical Analyst, Tim Anderson) everolimus and Abbott Labs' (ABT-$40.60; Neutral Weight Rated) zotarolimus on a stent because the FTC wanted to ensure that ABT would be a viable competitor in the drug-eluting stent (DES) market. ABT is currently developing a DES using its proprietary drug, zotarolimus which is also used on Medtronic's (MDT-$58.99; Overweight Rated) Endeavor DES. The clinical results for Endeavor have

been mixed thus far and data with ABT's DES, ZoMaxx, have not been presented yet so it's unclear how competitive ZoMaxx will be. Under the JNJ-GDT deal, ABT would be able to potentially develop a second DES using everolimus. Although ABT does not currently have the rights to use the drug everolimus on a stent from NVS, the drug's originator, it is our understanding that acquiring the rights would not be a major obstacle if ABT wanted to develop an everolimus-coated stent.

If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated or zotarolimus-coated stent. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board and the FTC pause for approving a BSX-GDT merger. According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,5857,64) patents.

Our analysis indicates that an offer of $78/share for GDT would be slightly more dilutive for JNJ on a cash and GAAP basis compared to its current $71/share offer but still accretive on a cash basis in 2008 (see merger models at the end of this note). In our model, we assume that JNJ raises the cash portion of its offer by $6/share. In addition, our analysis indicates that JNJ could offer $90/share for GDT before an acquisition of St. Jude is more attractive financially for JNJ (also shown at the end of this note).

VALUATION AND RISKS

Our price target of $59 is the average of our price targets for J&J with and without GDT. For JNJ alone, we apply a target multiple of 13.0x our 2008 EPS of $4.38 to arrive at a target price of $57. We use a multiple of 13x, a 7% discount to the average multiple of the large cap U.S. pharmaceutical group, which is appropriate in our view because of JNJ's slowing pharmaceutical growth (the source of 50% of JNJ's profits). We use 2008 EPS because that is the first year in which the GDT acquisition is expected to be accretive. For JNJ with GDT, we apply a target multiple of 14x our combined JNJ-GDT EPS estimate of $4.40 to arrive at a target price of $62. We use a multiple of 14x because this represents a 15% discount to our coverage universe which we believe is appropriate given the combined entity's below average growth prospects. Again, we use 2008 EPS because that is the first year in which the GDT acquisition would be accretive.

The average of the two scenarios yields a target price of $59.

Key risks to the achievement of our price target are: 1) less price erosion in the U.S. EPO market than we model; 2) branded and generic competition in the European EPO market takes less share of the market than we model; 3) Cypher captures greater market share from Taxus than what we model; 4) key pharmaceutical pipeline products such as paliperidone ER exceed our expectations; 6) JNJ acquires GDT; 7) JNJ's operating expenses grow more slowly than what we model; and 8) JNJ acquires additional late stage pharmaceutical products.

BUSINESS

Johnson & Johnson (JNJ), is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets

CHARTS/MODELS

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $71per Share (57% cash/43% stock)

In Millions, Except Per Share Data

Revenue Impact of GDT ($MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
JNJ Sales (ex-GDT)	$51.185	$53.819	$57.263	$60,996	$63.778	$68.791	6.0%	6.1%	6.3%
Total Incremental Sales (Guidant)	$3.549	$3,899	$4,479	$5,235	$5.942	$6,500	13.8%	12.9%	13.2%
Total JNJ GDT Pro Forma Sales	$54,735	$57.718	$61,742	$66.231	$69,720	$75.290	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1.254	1.591	1.860	2.132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expenses		820	1.231	1.551	1,807	2.079			
After Tax GDT Income		623	936	1.178	1.373	1.580			
Impact on JNJ Interest Income - After Tax		378	358	329	-293	-249			
Net Impact on JNJ Net Profit		**245**	**577**	**850**	**1.081**	**1,331**			

	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
Pre GDT JNJ EPS	3.49	3 74	4 09	4.38	4.52	4.98	7 9%	7.4%	6.8%
JNJ Cash EPS with GDT		**3.62**	**4.06**	**4.42**	**4.63**	**5.15**	8.2%	8.1%	8.2%
GDT Impact on Cash EPS		-0.11	-0.02	0.05	0.11	0.17			
Amort of Intang Per Share (Non Cash)		(0.16)	(0.16)	(0 16)	(0 16)	(0.16)			
JNJ GAAP EPS with GDT		$3.46	$3 90	$4.26	$4.47	$4 99			
GDT Impact on JNJ GAAP EPS		(0 27)	(0 19)	(0 12)	(0 05)	0 00			
Growth Impact of GDT									
Pre GDT JNJ EPS Y Y		7.1%	9.4%	7.1%	3 3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.9%	12.1%	8 9%	4 7%	11.1%			
Impact of GDT ex-Amort of Intangibles		3.2%	2.7%	1 8%	1 4%	1 0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		-0 8%	12 6%	9 3%	4 9%	11 5%			
GDT Impact on GAAP EPS Growth		-7 9%	3 3%	2 2%	1 6%	1.4%			

A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports
Assumes JNJ shares are worth $62 00

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $78 per Share (61% cash/39% stock)

In Millions, Except Per Share Data

Revenue Impact of GDT ($MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
JNJ Sales (ex-GDT)	$51.185	$53.819	$57.263	$60.996	$63.778	$68.791	6.0%	6.1%	6.3%
Total Incremental Sales (Guidant)	$3,549	$3,899	$4.479	$5,235	$5.942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma Sales	$54,735	$57,718	$61.742	$66.231	$69,720	$75.290	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1.591	1.860	2.132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expenses		820	1.231	1.551	1.807	2.079			
After Tax GDT Income		623	936	1.178	1.373	1.580			
Impact on JNJ Interest Income After Tax		458	439	-409	-373	-329			
Net Impact on JNJ Net Profit		**165**	**497**	**769**	**1,000**	**1.251**			

	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		**3.60**	**4.04**	**4.40**	**4.61**	**5.12**	8.0%	8.0%	8.3%
GDT Impact on Cash EPS		-0.14	-0.05	0.02	0.09	0.14			
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.44	$3.87	$4.23	$4.44	$4.96			
GDT Impact on JNJ GAAP EPS		(0.30)	(0.21)	(0.14)	(0.08)	(0.02)			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex Amort of GDT Intangibles		3.2%	12.2%	9.0%	4.8%	11.2%			
Impact of GDT ex-Amort of Intangibles		-3.9%	2.8%	1.8%	1.5%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		1.5%	12.7%	9.3%	4.9%	11.6%			
GDT Impact on GAAP EPS Growth		8.6%	3.3%	2.2%	1.7%	1.4%			

A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports
Assumes JNJ shares are worth $62.00

To view charts associated with those stocks mentioned in this report, please visit http://cm1.prusec.com.

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Larry Biegelsen is principally responsible for the analysis of any security or issuer included in this report and certifies that the views expressed accurately reflect such research analyst's personal views about subject securities or issuers and certifies that no part of his or her compensation was, is, or will be directly or indirectly related to the specific recommendation or views contained in the research report.

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When we assign an **Overweight** rating, we mean that we expect that the stock's total return will exceed the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign a **Neutral** Weight rating, we mean that we expect that the stock's total return will be in line with the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign an **Underweight** rating, we mean that we expect that the stock's total return will be below the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

ANALYST UNIVERSE COVERAGE:
Larry Biegelsen: Abbott Laboratories, Boston Scientific, Edwards Lifesciences, Johnson & Johnson, St. Jude Medical, Medtronic, Inc., Guidant Corp.
Tim Anderson, M.D.: Schering-Plough, Eli Lilly, Forest Laboratories, Merck & Co., Bristol-Myers Squibb, Wyeth, Pfizer, Inc., GlaxoSmithKline plc, AstraZeneca, Novartis AG, Roche Holding AG, Sanofi-Aventis Group.

Rating Distribution

01/19/06	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	29%	0%
Neutral Weight(Hold)*	48%	0%	53%	0%
Underweight(Sell)*	22%	0%	17%	0%

Excludes Closed End Funds

12/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	31%	0%
Neutral Weight(Hold)*	47%	0%	52%	0%
Underweight(Sell)*	23%	0%	17%	0%

Excludes Closed End Funds

09/30/05		Firm's		Sector's

Healthcare
Medical Devices

	Firm	Investment Banking Clients	Sector	Investment Banking Clients
Overweight(Buy)*	32%	0%	29%	0%
Neutral Weight(Hold)*	44%	0%	49%	0%
Underweight(Sell)*	24%	0%	22%	0%

Excludes Closed End Funds

06/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	32%	0%	31%	0%
Neutral Weight(Hold)*	45%	0%	51%	0%
Underweight(Sell)*	22%	0%	19%	0%

Excludes Closed End Funds

* In accordance with applicable rules and regulations, we note above parenthetically that our stock ratings of "Overweight," "Neutral Weight," and "Underweight" most closely correspond with the more traditional ratings of "Buy," "Hold," and "Sell," respectively; however, please note that their meanings are not the same. (See the definitions above.) We believe that an investor's decision to buy or sell a security should always take into account, among other things, that the investor's particular investment objectives and experience, risk tolerance, and financial circumstances. Rather than being based on an expected deviation from a given benchmark (as buy, hold and sell recommendations often are), our stock ratings are determined on a relative basis (see the foregoing definitions).

Prior to September 8, 2003 our rating definitions were Buy, Hold, Sell. They are defined as follows:

When we assign a **Buy** rating, we mean that we believe that a stock of average or below-average risk offers the potential for total return of 15% or more over the next 12 to 18 months. For higher-risk stocks, we may require a higher potential return to assign a Buy rating. When we reiterate a Buy rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

When we assign a **Sell** rating, we mean that we believe that a stock of average or above-average risk has the potential to decline 15% or more over the next 12 to 18 months. For lower-risk stocks, a lower potential decline may be sufficient to warrant a Sell rating. When we reiterate a Sell rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

A **Hold** rating signifies our belief that a stock does not present sufficient upside or downside potential to warrant a Buy or Sell rating, either because we view the stock as fairly valued or because we believe that there is too much uncertainty with regard to key variables for us to rate the stock a Buy or Sell.

When we assign an industry rating of Favorable, we mean that generally industry fundamentals/stock prospects are improving.

When we assign an industry rating of Neutral, we mean that generally industry fundamentals/stock prospects are stable.

When we assign an industry rating of Unfavorable, we mean that generally industry fundamentals/stock prospects are deteriorating.

Healthcare
Medical Devices

Ratings History: JNJ

Rating Changes			
Date	From	To	Analyst
12/08/05	--	UNDR	Biegelsen
03/31/05	OVER	--	Faulkner
08/20/04	--	OVER	Faulkner

Target Price Changes			
Date	From	To	Analyst
12/08/05	--	59 00	Biegelsen
03/31/05	74 00	--	Faulkner
12/16/04	61 00	74 00	Faulkner
08/20/04	--	61 00	Faulkner

Additional Information

Price Target – Methods/Risks

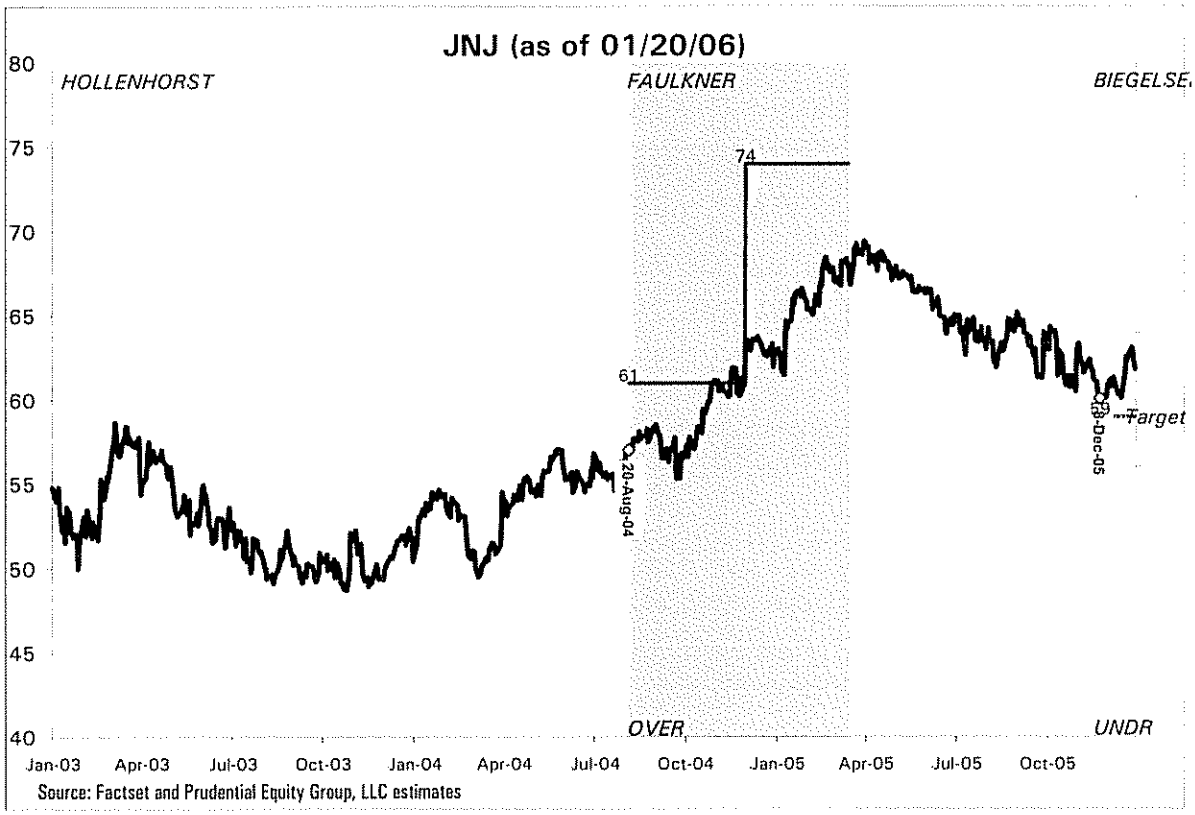
The methods used to determine the price target generally are based on future earning estimates, product performance expectations, cash flow methodology, historical and/or relative valuation multiples. The risks associated with achieving the price target generally include customer spending, industry competition and overall market conditions.

Additional risk factors as they pertain to the analyst's specific investment thesis can be found within the report.

Price History: JNJ

January 20, 2006

Healthcare
Medical Devices



January 20, 2006

Healthcare
Medical Devices

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EXHIBIT E

January 23, 2006

HEALTHCARE INDUSTRY NOTE

The Game May Be Far from Over

Disclosure Information: Please see pages 5 - 12 of this report for important disclosure information.

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HEALTH CARE

We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over. Both companies seem intent on winning the battle for GDT, even to the extent of being 'nice' to sell side analysts. Our takeaway message from these conversations has been that both sides believe there is information to share that can bolster the argument for its being a better suitor for GDT.

JNJ, for example, reminded us that the analysis that BSX presented as to its valuation included price objectives that did not assume the deal had taken place. That is certainly true of our $42 price objective, which is built on our beliefs about the dynamics of the drug eluting stent market and BSX's potential pipeline of products (moving to the right in time and leaving some unsuccessful projects behind to be sure, assuming its deal with GDT goes through). Suffice it to say, we were glad that BSX did not just use our Price Objective, but averaged it with others.

We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 and 6585764), and, sure enough, both have to do with using any '-limus' on a stent. We have not vetted these patents, but they did seem quite broad in their language. When we spoke to BSX management about them, we were told neither GDT nor Abbott (ABT) seemed to be concerned about them, and that their broad language may make them non-defensible. As we said, we have not vetted them yet.

Here Are Our Initial Thoughts for Potential EPS, Assuming Things Go Through as BSX Has Planned

As for our conversation with BSX, we were surprised, somewhat, by the conservative assumptions it was making on stent market share (it was trying to keep to Street assumptions) and especially on GDT high voltage market share (we had been presuming, as has the Street, a faster ramp to normalcy). BSX is assuming that GDT only will have 26% share exiting '07, 25% in mid-'07 and 24% in 4Q06. Because of this we are assuming the company earns $0.90 in '06, $1.35 in '07, $1.80 in '08 and $2.35 in '09 on a pro forma basis, assuming the BSX/GDT merger goes through as planned. We believe the company's internal estimates are lower than these. We discuss how we derived these estimates in more detail later on in this piece

We also would like to remind investors that this analysis and all subsequent analysis on this piece are based on the assumption that BSX does indeed merge with GDT at the $80 price recently submitted by BSX. JNJ has yet to respond to this new bid by BSX and it may do so. As a result, investors should view this analysis as speculation based on what we know at this time. **Since this is speculation, we are maintaining our price objective and estimates at this time as we have no assurances that BSX will end up with GDT.** It is still a pretty dynamic atmosphere out there in our view.

Additional Synergies with BSX/GDT? Perhaps.

BSX also told us that there were more potential synergies than it had initially expected. It has said that it expected $400 million in synergies, $200 million from the GDT side and $200 million from its side, mainly from reducing corporate overhead and only having to have 1.2x the international

infrastructure that it currently has. It has also determined that there are between $50 million and $100 million of manufacturing savings that can be realized as well (especially in inspection, scrap and waste). We are not surprised by this. Our experience at GDT was that manufacturing efficiency, while taken seriously, was not taken as seriously as it has been at BSX.

As far as the arrangements with ABT is concerned (ABT, if BSX ends up with GDT, would purchase GDT's vascular business and share rights to GDT's drug eluting stent program. It also would own a portion of BSX, approximately 4%), it appears that ABT was the only true candidate for the rapid exchange technology or the larger deal that BSX is proposing. This would imply that the FTC is probably agreeable to the plan being offered, so it is more of a matter of time than worrying about the structure of the planned acquisition. We do believe that a definitive offer will likely have to be in place prior to the deal being closed. We also think that it will be late 2008/early 2009 before we see a combination product in the market.

Interesting times these.

Our Numbers Analysis, at Least on a Theoretical Basis

Now that it is BSX' turn at bat in the battle for GDT (JNJ may be heard from before Wednesday), we thought we would take a look at what BSX's value might be after any such merger. However, **investors should keep in mind once again that this exercise is theoretical**, as GDT has yet to recommend BSX's bid and we have not heard back from JNJ who, again, could come back with a new bid itself. BSX did give some level of guidance of what it might expect to see in terms of EPS after a potential merger when it bid $72 per share for GDT. At that time, BSX stated that we could expect EPS to be in a rage of $1.50 to $1.66 in 2007 and $1.98 to $2.18 in 2008.

A lot has changed since that time, however due to BSX's $80 bid for GDT. While we think BSX wisely sold some equity to Abbott (ABT) in its latest bid, which resulted in less debt being accumulated, there still should be some additional incremental debt it has taken on (around $200 million) and potential EPS dilution from those new shares being sold to ABT

Back to the Pre-Taxus Days in Terms of Expense Control?

However, in our subsequent discussions with the company, it indicated a willingness to return to "pre-Express/Taxus" spending disciplines, assuming that it succeeds in its efforts to acquire GDT. Remember before the Express stent (the bare metal platform that BSX developed internally before the DES era), BSX was suffering from an extended period of market share losses (down to 8% of the market by our reckoning) and lackluster top line growth.

We think that cost control at this point is important. During past analyst meetings BSX indicated that it wanted to keep its after tax margins below 30% as it believed that it had a number of projects it could invest in both internally and externally (and it mentioned at the time, we think correctly, that investors would not reward it for a relatively high after tax margin). Our question is how deeply will BSX reign in costs assuming that its operations are already relatively efficient, as evidenced by operating margins often in excess of 30%? After speaking with the company on Friday, it is apparent that it does intend to slow down expenditures, because, as the management put it, now that we would have GDT's pipeline and R&D efforts, we may be able to slow down or stop expenditures related to longer-term projects. We should all remember that BSX has been spending approximately $600 million or more on milestone payments and new technology projects in addition to its in-house R&D expenditures. With a new focus, having acquired GDT, these projects will be reviewed and some of them most likely terminated.

We May See Dilution Until FY10, in This Scenario

Regardless of the synergies the company finds in these R&D programs, BSX's EPS should be diluted until FY10, at least according to our analysis and our assumptions so far. We are assuming that in the DES market that BSX retains its entire market share that we assumed it would get before the merger (approximately 30%) and we layered on top of that a portion of what we assumed would be GDT's market share. **This analysis and all subsequent analysis in this piece, again, is predicated on BSX succeeding in obtaining GDT, which we think is not a sure thing** as we have not definitively heard from JNJ as of yet.

Going into more detail, we originally assumed that GDT would also achieve approximately 30% of the DES market by the end of the decade. Taking that figure we assumed that BSX and ABT would split 40% of that market share each, with the remainder going to JNJ, due to continuity of JNJ's operations and marketing teams (sorry, MDT). The company has told us that it is assuming that two-thirds of the market share will be incrementally derived, and

one-third from cannibalization. The numbers work out to be almost equivalent. We are going to stick with our analysis. It's easier on the eyes.

We further assumed that BSX would have most of its integration issues behind it by late FY08 to early FY09 with its operating margins starting to return to normalcy (30%+). The company is actually more conservative and assumes that it will not reach that goal until close to FY10. We are also assuming that GDT's CRM group slowly returns to close to a 30% market share range in high voltage in the United States by the end of the decade. However, due to GDT related debt, integration costs and additional shares that BSX has offered, it emerges from earnings dilution around FY10 in our model. Preliminarily, we assume that BSX's pro-forma earnings may approximate $0.90 for FY06, $1.35 for FY07, $1.80 for FY08 and $2.35 for FY09. Once again, this is predicated on the assumption that BSX acquires GDT, and all of this analysis may change quickly if JNJ comes in with a competing bid.

Here's Our Initial Take on a Theoretical Valuation, But the Game Might Not Be Over Yet. Keeping those assumptions and qualifiers in mind, recently our peer group average for BSX (MDT, EW, STJ) was trading at a one year forward multiple of 25.6x. The question we believe worth asking, is what should be the discount to that multiple? Using that average with no discount leads us to a valuation of $35 per share, utilizing our preliminary FY07 estimate. We decided to use FY07 as opposed to the one year forward (FY06) as FY07 would be the first full fiscal year with GDT under its belt as well as the first year it may begin to move toward normalcy. However, we do believe that BSX should receive some discount due to the potentially higher short-term financial risk the company might face. The problem is that we cannot think of any recent acquisitions of this size and scope among equals that is dilutive over the course of a couple years in this or any other industry. Therefore any number we pick as a discount rate would be somewhat arbitrary.

Since we were unsure on what discount to that multiple should be, we decided to create a table of discount values to determine a valuation range and then make an more educated estimate on what a potential valuation might be using our recent comp group EPS multiple of 25.6x as a base.

	Discount Rates			
EPS Ests	10%	20%	30%	40%
$1.15	$26.50	$23.55	$20.61	$17.66
$1.25	$28.80	$25.60	$22.40	$19.20
$1.35	$31.10	$27.65	$24.19	$20.74
$1.45	$33.41	$29.70	$25.98	$22.27
$1.55	$35.71	$31.74	$27.78	$23.81

Source: A.G. Edward theoretical estimates.

Using the middle portion of this table as a proxy for potential outcomes, we see a range of potential values of $30 to $22 per share. This fits in within our preliminary pro-forma discounted cash flow analysis of approximately $28 per share. In that analysis, we used all of the EPS assumptions listed above as well as weighted average cost of capital of 12.0%, an implied market risk for the shares of 10.5% (our large cap universe range is 7.5% to 11.0%) and a long-term growth rate of 12%.

However, we would also like to stress that this is a preliminary analysis. We expect to see and hear more from BSX, GDT and possibly JNJ in the coming days. Our intention is to give investors an idea of what might be, given events could change very quickly. Importantly, we are sticking with ourl price objective for BSX of $42 per share and our current estimates as we do not believe this saga is near completion at this time.

Boston Scientific (BSX – $23.34 – Buy/Aggressive) Valuation

We use a three-stage discounted cash flow model, which leads us to a price objective of $42 per share. Our weighted average cost of capital was 11.3%. Our market risk premium is 9%. We assumed a free cash flow growth rate of 11.75% for 10 years after our detailed cash flow model ends in 2010 and assume a growth rate of 4% thereafter. On a P/E basis, BSX's one-year forward P/E five-year average is 28.8x with a range of 70.7x to 12.0x. Based upon our FY06 estimate of $1.82 and our price objective of $42, we have a target P/E value of 23.0x, a discount to its five-year average, but appropriate in our opinion as we think BSX has a good long-term pipeline.

BSX Risks To Valuation

Risk to achieving our price objective include unanticipated market share losses in the drug-eluting stent market (e.g., new competitive products being more successful than we anticipate, product recalls, etc.), new products not being successfully brought to market or not experiencing sales levels as highs as we anticipate, regulatory risk (e.g., reimbursement and regulatory approval), ongoing

litigation risk and the highly competitive markets in which the company competes

Guidant (GDT – $76.00 – Hold/Speculative)
Valuation
We use a three stage discounted cash flow model for our valuation. Our discount rate on our future cash flows, which is the weighted average cost of capital, we are using is 12.1%. This and other assumptions lead us to believe GDT is at fair value. Based upon our FY06 estimate of $1.70 per share, GDT is now trading at a P/E multiple of 44.8x.

GDT Risks To Valuation
The ongoing issues and uncertainties we have seen in the stent business are the major risks for Guidant. Others include acquisition risks, slower than expected uptake of CHF devices, new technology not only from direct competitors, but also from other sectors as well such as Pharma, regulatory risk, reimbursement risk and litigation risk.

Johnson & Johnson (JNJ – $61.19 – Hold/Conservative) Valuation
We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption at the time of analysis was 10.4%, we assumed a free cash flow growth rate of 9.0% for 10 years after our detailed forecasts embedded in our model end in FY10, and 4.0% thereafter. These and other assumptions lead us to believe that the shares are at a level that represents what we would consider fair value. On a P/E basis, JNJ's two-year forward P/E five-year average is 20.0x with a range of 27.7x to 15.2x. Based upon our FY06 estimate of $3.80, JNJ is currently trading at a P/E (at a recent price of $61.19 per share) of 16.1x. We believe that a multiple at the lower end of the range is justified due to competition in the drug-eluting stent marketplace, and potential and existing generic competition in some product lines in pharma.

JNJ Risks To Valuation
Johnson & Johnson may see greater competition than expected in the drug-eluting stents market in the United States, and new drug-eluting stent products from competitors in Europe. The Pharma pipeline may be weaker than expected, and there may be increased competition from generic manufacturers.

Abbott Labs (ABT – $40.51 – Buy/Aggressive) Valuation
We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption is 11.5% and our risk premium assumption is 9%. Our out year operating cash flow growth assumption is 11.0% for ten years (2011-2020)-right in the middle of the largest of our large-cap group. These and other assumptions lead us to our price objective of $46 per share. On a P/E basis, using our $2.70 FY06 EPS estimate, and our $46 price objective the multiple is 17.0x. This compares to a five-year historical two-year forward P/E average of 18.3x, with a range of 13.4x to 25.2x. We feel that our implied target multiple, which is close to its historical average, is justified due to uncertainty concerning generic competition, but offset by good potential we see in Medical Products. Therefore, being close to the middle seems like a good place to be.

ABT Risks To Valuation
Risks to achieving our price objective include the fact that Abbott's pharmacological pipeline may not be as robust as we have assumed, sales of its key products (such as Humira) may not be as strong as we anticipate and it participates in highly competitive and regulated markets.

Analyst Certification Statement
The views expressed in this research report accurately reflect my personal views about the subject company/companies and securities. I receive no compensation that is directly or indirectly related to the specific recommendations or views contained within this report.

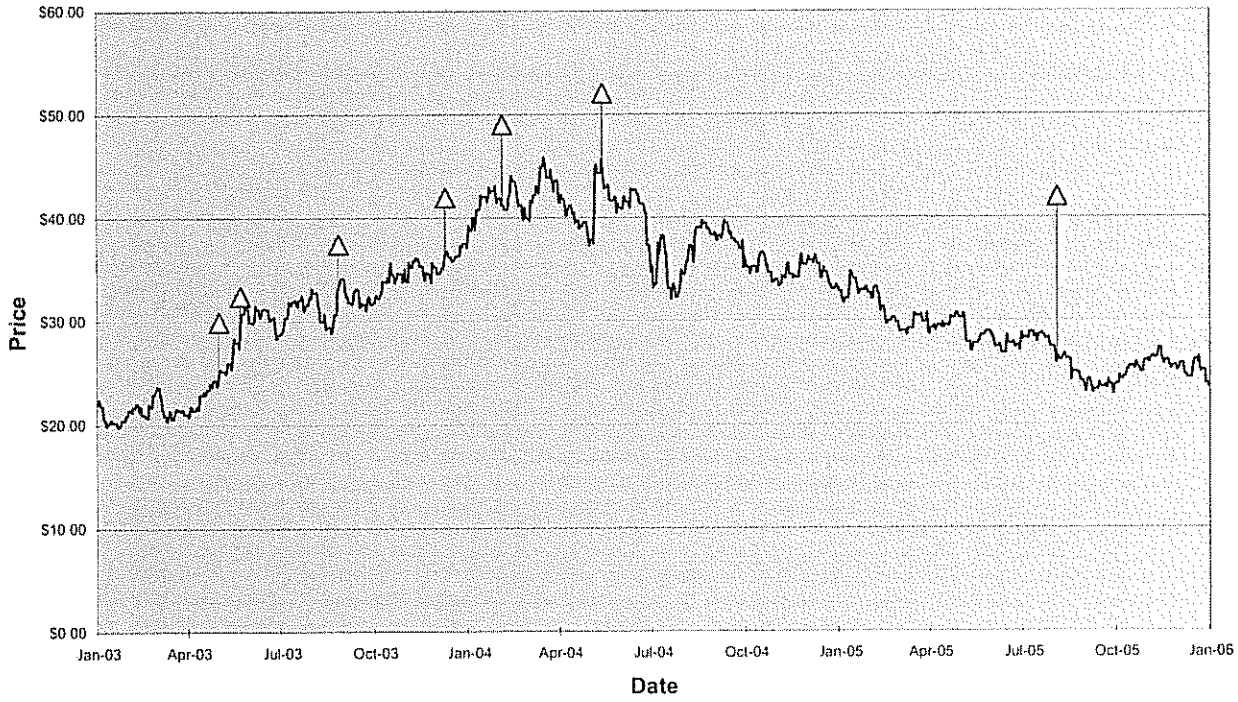
All prices from intraday on 1/230/6.

BOSTON SCIENTIFIC

EDWARDS.

January 21, 2006
Buy/Aggressive
BSX/NYSE/$23.59

Price Objective: $42.00



Pricing sources: Factset and IDSI

Daily Closing Prices
Price Objective Changes
Rating/Suitability Changes
Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		25.00	09/16/2003	33.25	37.50	06/02/2004	44.70	52.00
05/21/2003	25.04	30.00	12/30/2003	36.54	42.00	08/24/2005	26.38	42.00
06/11/2003	29.88	32.50	02/24/2004	41.27	49.00			

* NA: Positive rating removed; no price objective supplied

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Strong Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D Wald	01/18/2001				

BOSTON SCIENTIFIC

EDWARDS

January 21, 2006
Buy/Aggressive
BSX/NYSE/$23.59

Price Objective: $42.00

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%) Total return expectations should be higher for stocks which possess greater risk

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated

Sell: Stock should be sold. as a materially negative total return is anticipated

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability. balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market

Aggressive: Fundamental risk is higher than the market

Speculative: Fundamental risk is significantly higher than the market

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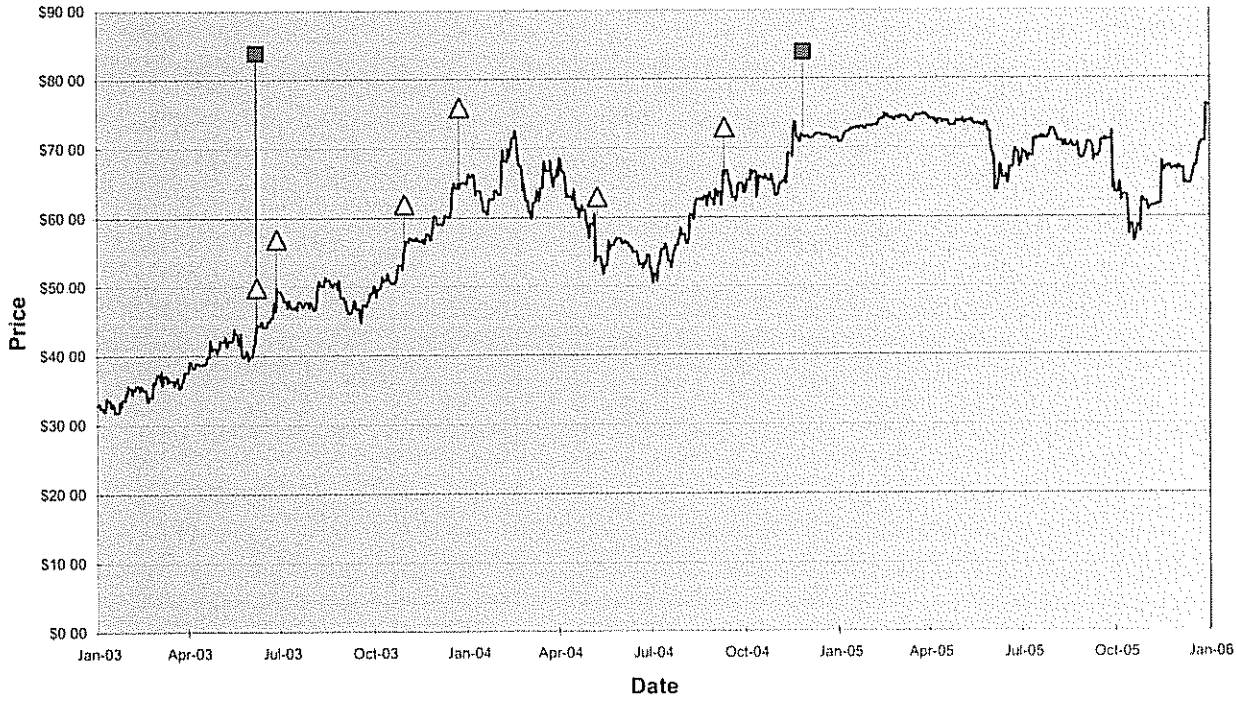
GUIDANT CORP

EDWARDS.

January 21, 2006
Hold/Speculative
GDT/NYSE/$75.95



Pricing sources: Factset and IDSI

Daily Closing Prices
Price Objective Changes
Rating/Suitability Changes
Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		NA	11/20/2003	55 35	62 00	09/30/2004	66 04	73 00
06/27/2003	44 51	50 00	01/13/2004	64 28	76 00	12/17/2004	71 62	NA
07/17/2003	49.96	57.00	05/28/2004	54 34	63 00			

* NA: Positive rating removed; no price objective supplied

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Hold/Speculative	12/17/2004	71 62	Hold/Speculative
06/27/2003	44 51	Buy/Speculative			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	01/08/2001				

GUIDANT CORP

EDWARDS.

January 21, 2006
Hold/Speculative
GDT/NYSE/$75.95

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
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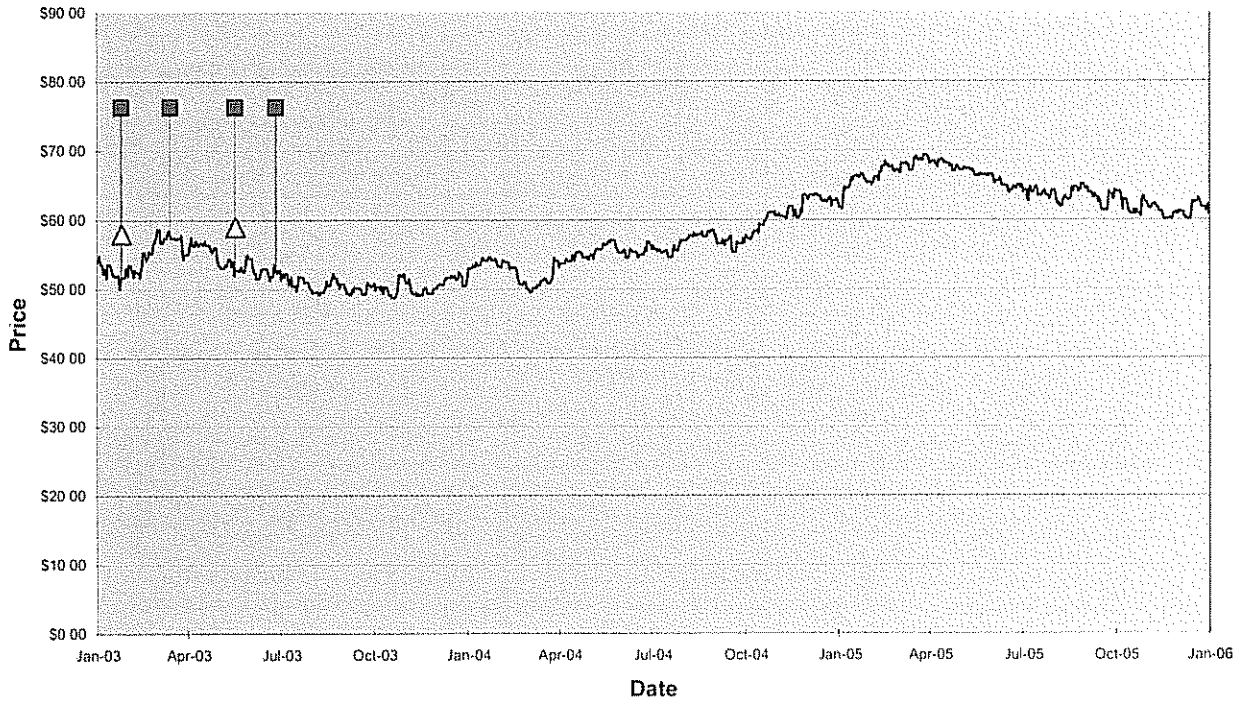
JOHNSON & JOHNSON

EDWARDS.

January 21, 2006
Hold/Conservative
JNJ/NYSE/$60.80



Pricing sources: Factset and IDSI

Daily Closing Prices
Price Objective Changes
Rating/Suitability Changes
Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		NA	04/03/2003	57 46	NA	07/16/2003	52 60	NA
02/14/2003	51 75	58 00	06/06/2003	52 75	59 00			

* NA: Positive rating removed; no price objective supplied

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Hold/Conservative	06/06/2003	52 75	Buy/Conservative
02/14/2003	51 75	Buy/Conservative	07/16/2003	52 60	Hold/Conservative
04/03/2003	57 46	Hold/Conservative			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

JOHNSON & JOHNSON

EDWARDS

January 21, 2006
Hold/Conservative
JNJ/NYSE/$60.80

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
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The subject company is or was a client of AGE during the past 12 months for non-investment banking securities-related services and analyst is aware of same
AGE and/or officer(s) own a long position in the issuer's equity securities

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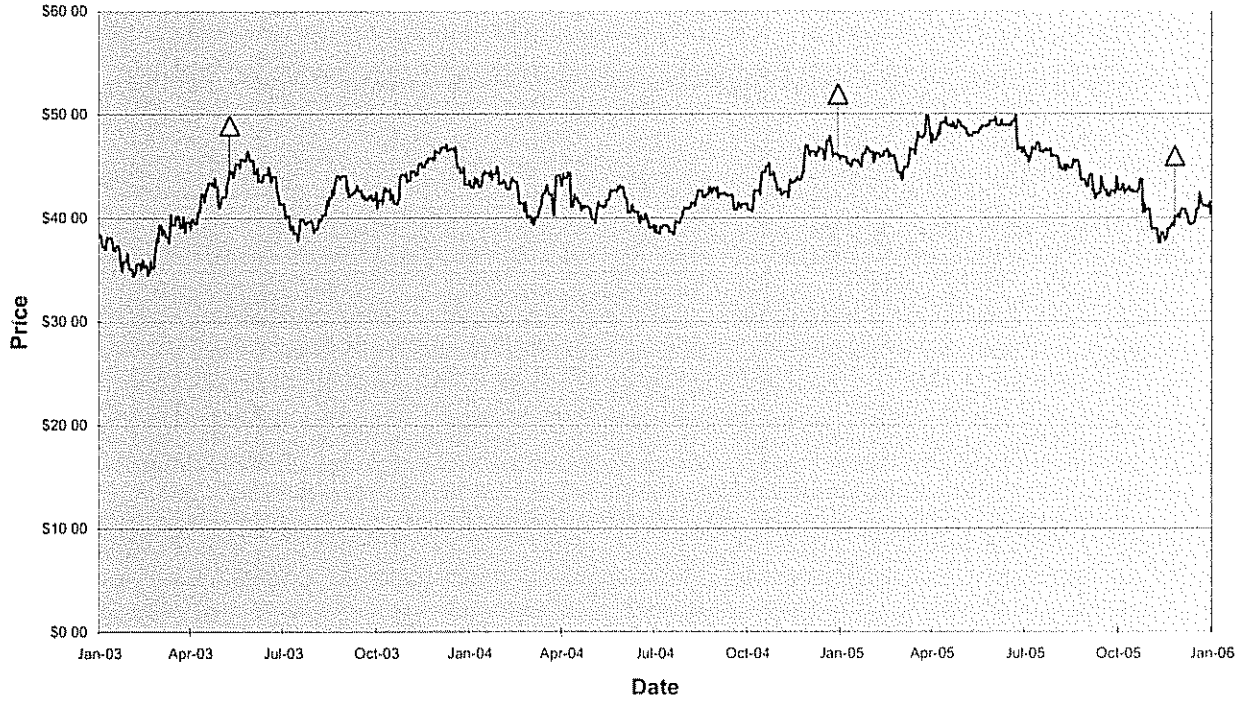
ABBOTT LABORATORIES

EDWARDS.

January 21, 2006
Buy/Aggressive
ABT/NYSE/$40.35

Price Objective: $46.00



Pricing sources: Factset and IDSI

Daily Closing Prices
Price Objective Changes
Rating/Suitability Changes
Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		46.00	01/18/2005	46.04	52.00			
05/30/2003	44.55	49.00	12/16/2005	40.17	46.00			

* NA: Positive rating removed; no price objective supplied

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

ABBOTT LABORATORIES

EDWARDS

January 21, 2006
Buy/Aggressive
ABT/NYSE/$40.35

Price Objective: $46.00

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Not applicable

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EXHIBIT F

INTERNATIONAL
Herald Tribune

J&J works to discredit rival offer for Guidant

By Avram Goldstein Bloomberg News
MONDAY, JANUARY 23, 2006

WASHINGTON Johnson & Johnson, facing a deadline on Tuesday for raising its bid to acquire the cardiac device maker Guidant, is trying to sow doubts among investors about Boston Scientific's rival offer, according to analysts

Johnson & Johnson, the world's biggest maker of medical devices, and its advisers told securities analysts last week that Boston Scientific would borrow too much for the deal, according to analysts at Prudential Equity Group and A G Edwards

J&J also said Boston Scientific had been making unrealistic financial projections to justify its $27 billion offer to buy Guidant, almost $3 billion more than Johnson & Johnson's

"J&J is communicating to the Street that Boston Scientific's $80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday. The campaign, he said, suggests "that J&J is still very interested in acquiring Guidant and that J&J will likely increase its offer at least one more time "

The Guidant transaction would be the biggest purchase of a medical device company Guidant, the second-largest maker of implantable defibrillators and pacemakers, behind Medtronic, is developing a cardiac stent that would pose a competitive threat to rival products of J&J and Boston Scientific, the world's biggest maker of heart stents, tiny metal sleeves used to clear artery blockages

A spokesman for J&J, Jeffrey Leebaw, and for Guidant, Steven Tragash, declined to comment

J&J shares fell $1 37, or 2 2 percent, to close last week at $60 80 in New York Stock Exchange composite trading Guidant dropped 17 cents, to $75 95 Boston Scientific declined 36 cents, or 1 5 percent, to close at $23 59

Guidant said Tuesday that Boston Scientific's offer of about $27 billion, or $80 a share, of which $42 would be in cash and $38 in stock, was "superior" to J&J's bid of $24 2 billion, or $71 a share, consisting of $40 52 in cash and the rest in J&J shares

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A G Edwards Wald said he had been called by a Johnson & Johnson employee, whom he declined to name

Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential

Drug coatings on stents are designed to keep tissue growth from clogging blood vessels again

Abbott agreed to contribute $6 4 billion to the Boston Scientific bid and acquire Guidant's vascular business including the new cardiac stent

Abbott shares lost $1 19, or 2 9 percent, on Friday to close the week at $40 35

Patent infringement lawsuits over stent drug coatings have "no bearing on our proposed acquisition of Guidant," a spokesman for Boston Scientific, Paul Donovan, said "Unfortunately, threats of legal action are commonplace in our industry "

Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design At the moment, the two companies are alone in the U S stent market, with Boston Scientific holding a 55 percent share

Abbott, Guidant and Medtronic are all developing competing products coated with drugs similar to the one that Johnson & Johnson's stent uses

The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" Abbott's zotarolimus and Guidant's everolimus, he wrote

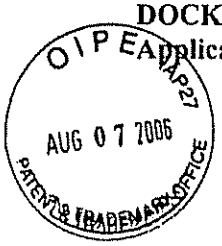
After the Guidant board declared Boston Scientific's bid superior, Johnson & Johnson issued a statement calling the proposal a "highly dilutive and leveraged transaction based on extremely aggressive business projections "

The statement said the Boston Scientific bid "will not provide $80 per share in value to Guidant shareholders "

Boston Scientific initially bid $25 billion on Jan 8, a month after declaring its intention to make an offer

EXHIBIT G

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: **7537**

Application No.: **10/951,385**

Group Art Unit: **3731**

Filing Date: **September 28, 2004**

Examiner:

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

08/09/2006 HDESTA1 00000002 10951385
01 FC:1464 130.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and

b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385

☐ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No 23-3050.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: **7537**

Application No.: **10/951,385**

Group Art Unit: **3731**

Filing Date: **September 28, 2004**

Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 64 to 140 are presently pending. Claims 64 and 103 are the only independent claims. Claim 103 is directed to a device comprising a metallic stent, a biocompatible polymeric carrier and a drug. The drug is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation. Claim 130, which depends from claim 103, specifies that the drug is a macrocyclic lactone analog of rapamycin.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3) Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V

product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

7. In a release dated September 21, 2005 (Exhibit 5), Guidant states that XIENCE™ V is being utilized in SPIRIT II and SPIRIT III clinical trials to evaluate the safety and efficacy of the product for the treatment of coronary artery disease. XIENCE™ V is described as "an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium MULTI-LINK VISION® Coronary Stent System platform." In an earlier release, dated April 5, 2004 (Exhibit 6), Guidant stated that it "holds a worldwide exclusive license . . . to use everolimus, a novel proliferation-signal inhibitor with potent anti-proliferative and immunosuppressant properties, in drug eluting stents." The April 5, 2004, release also states that "Guidant has both durable and bioabsorbable polymer drug carriers in development" and that "[t]he company's clinical trials utilizing durable polymer technology are identified by the SPIRIT designation in the study name." In the same press release, the MULTI-LINK VISION® Coronary Stent System is referred to as a "market-leading metallic stent." On the basis of these statements made by Guidant, I conclude that the XIENCE™ V product comprises a metallic stent coated with everolimus and a durable polymer carrier.

8. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 7, 8). In a press release dated March 15, 2006 (Exhibit 9), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 10), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product contains a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

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ABOUT US
Corporate Overview
Locations
Global Compliance
Guidant Foundation
Careers
Newsroom
Historical Investor Resources

Guidant Receives European Approval for Drug Eluting Coronary Stent

Company Achieves CE Mark Approval Ahead of Schedule; XIENCE V Launch Slated for Second Quarter

Indianapolis, Ind. and Brussels — January 30, 2006 — Guidant Corporation (NYSE: GDT) today announced that the company has received Conformité Européene (CE) Mark approval for the XIENCE™ V Everolimus Eluting Coronary Stent System. This regulatory certification allows Guidant to begin marketing the drug eluting stent in the 25 countries of the European Union. In addition, the CE Mark Approval is used to support market registrations in other regulated countries including those within Asia, Latin America and Eastern Europe.

"This early approval represents a significant milestone in Guidant's drug eluting stent program and demonstrates our ongoing commitment to advancing the field of cardiovascular therapy through innovative solutions," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "The development of XIENCE V represents years of hard work and dedication by our employees and by trial investigators. We look forward to bringing this next-generation therapy to physicians and patients."

The XIENCE V Everolimus Eluting Coronary Stent System utilizes Guidant's most advanced coronary stent system, the highly deliverable cobalt chromium MULTI-LINK VISION®, which is available on the preferred rapid-exchange platform. Everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation.

"Completion of the CE Mark approval process for XIENCE V follows on the heels of impressive clinical results from the SPIRIT FIRST trial, which demonstrated the benefits of an everolimus drug eluting stent," said Prof. Patrick W. Serruys, M.D., of the Thoraxcenter, Erasmus University Hospital, Rotterdam, who served as the study's principal investigator. "With this approval, physicians in Europe will have an excellent treatment option for patients requiring a drug eluting stent."

Guidant is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE V beginning in the second quarter of 2006.

In November, Guidant announced completion of enrollment in only four months of SPIRIT II, a 300-patient, randomized clinical trial evaluating XIENCE V. The single-blind, prospective, randomized, non-inferiority study further evaluates the XIENCE V compared to the TAXUS® Express 2™ Paclitaxel-eluting coronary stent system for the treatment of coronary artery disease.

Guidant's 1,380-patient SPIRIT III global clinical trial is evaluating the XIENCE V Stent System in the United States and Japan. The randomized U.S. cohort, which will support U.S. Premarket Approval submission, has enrolled more than 70 percent of the required patients and is expected to complete enrollment later this quarter.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life

today to millions of cardiac and vascular patients worldwide. The company develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com

This release includes forward-looking statements concerning XIENCE V. The statements are based on assumptions about many important factors, including satisfactory enrollment and completion of the clinical trial, associated regulatory processes and timelines, and other factors identified on Exhibit 99 to the company's most recent filing on Form 10-Q Actual results may differ materially. The company does not undertake to update its forward-looking statements.

<< Back

EXHIBIT 2

Print this page

Guidant Provides Update

Indianapolis, Ind. — October 19, 2005 — Guidant Corporation (NYSE: GDT), a world leader in the treatment of cardiac and vascular disease, today responded to statements by Johnson & Johnson on its pending acquisition of the Company and provided an update on its two major businesses.

Transaction Update

In response to Johnson & Johnson's comments yesterday, Ronald W. Dollens, president and CEO of Guidant Corporation, stated, "While neither company depends on this transaction for its continued future success, Guidant believes that the strategic rationale for combining the two companies is as strong today as when we entered into the Merger Agreement." Guidant anticipates that the pending transaction will receive FTC clearance in October. The Company does not expect to make any specific comments on the pending transaction until after FTC approval.

Business Performance

"Guidant's third quarter results will reflect the temporary unavailability of the CONTAK RENEWAL 3 and 4 family of heart failure devices during the full month of July and part of August, partially offset by sequential growth of U.S. coronary stent revenue, and continuing sales growth of our emerging businesses," Dollens reported. "At the end of the quarter, data suggest our implantable defibrillator implant rate exceeded 80 percent of the pre-product notification level and is over 100 percent of the rate one year ago."

Dollens continued, "As previously announced, Guidant is launching several recently approved cardiac rhythm management systems during the fourth quarter, including the revolutionary Latitude Patient Management system. Physicians are expressing enthusiasm for the new wireless capability to monitor patients, improve their compliance, and monitor device status independent of patient effort." Dollens further observed, "Our drug eluting stent development program continues to make important progress toward European launch during the first half of next year. We are expanding manufacturing capacity, increasing productivity, and recently received FDA approval to expand clinical trial enrollment."

"While recent events and the publicity surrounding them will impact our short-term results, we believe that the fundamentals of our business and the markets that we serve remain strong and our outlook is positive," Dollens noted. "Our track record of success over the years has been driven in large part by the dedication of our people to the needs of patients and physicians who use our products. We continue to be committed to providing the highest quality products for patients who critically need them and we are confident that the value of the Company remains strong."

Cardiac Rhythm Management Products Update

Consistent with an anticipated new product cycle, several significant new products were approved (cleared) by FDA during the third quarter. They include:

- VITALITY HE implantable defibrillator; Guidant's first high-energy product to offer the advanced functionality of the VITALITY family.
- CONTAK RENEWAL 3 RF cardiac resynchronization-defibrillator; this is Guidant's first wireless and wandless CRT-D and is designed to enhance the speed and convenience of patient care.
- ZOOM LATITUDE programmer; this next generation programmer is designed to interface with devices that include remote monitoring capability.

- LATITUDE Communicator and secure data storage system; these elements represent the final components of the Latitude Patient Management system.

Actions taken by the Company during the quarter reflect Guidant's commitment to provide more timely information to physicians and patients about our devices. Our products continue to demonstrate high performance and reliability, and tens of thousands of people are alive today and hundreds of thousands feel better as a result of Guidant's technologies. Guidant will continue to focus on meeting and exceeding the expectations of physicians, patients and the FDA.

Drug Eluting Stent Progress

Guidant announced today that its drug eluting stent development program continues to demonstrate progress and the Company has enrolled more than 500 patients in the SPIRIT II and III clinical trials since June. SPIRIT III is a large-scale pivotal clinical trial evaluating XIENCE™ V, an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium rapid-exchange MULTI-LINK VISION® RX Coronary Stent System platform. Guidant plans to use the results of the SPIRIT III trial to obtain FDA approval for XIENCE V for the treatment of coronary artery disease. Results of the SPIRIT II study will provide additional clinical data to support the launch of XIENCE V in Europe and several countries outside the United States.

Earlier in the quarter, Guidant announced attainment of an enrollment milestone in the Company's exclusive license agreement with Novartis Pharma AG. Novartis supplies everolimus to Guidant for use in drug eluting stents and provides access to data supporting Guidant filings with regulatory agencies.

In addition, the Company plans to present one-year follow up data from SPIRIT I at the American Heart Association meeting in November 2005. SPIRIT I is a prospective, randomized, single-blind pilot study evaluating XIENCE V versus an uncoated MULTI-LINK VISION Coronary Stent System control in de novo (previously untreated) lesions.

During the quarter, the Company also announced that it successfully concluded an inspection of its drug eluting stent manufacturing and quality systems at its Temecula site. This inspection was conducted by Guidant's European Notified Body, which is also reviewing the Company's submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. The Notified Body found no nonconformities and will recommend certification for Guidant's manufacturing facility.

Guidant Corporation

Guidant Corporation pioneers lifesaving technology, giving an opportunity for a better life today to millions of cardiac and vascular patients worldwide. The Company, driven by a strong entrepreneurial culture of more than 12,000 employees, develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information, visit www.guidant.com.

This release includes forward-looking statements that are based on assumptions about many important factors, including market trends and competition, particularly in connection with expanded indications and reimbursement for cardiac rhythm management products; satisfactory clinical and regulatory progress; progress with respect to the merger, including satisfaction of conditions to closing, including antitrust approvals; economic conditions, including exchange rates; litigation developments; and the factors listed on exhibit 99 to Guidant's most recent 10-Q. As such, they involve risks that could cause actual results to differ materially. The company does not undertake to update its forward-looking statements.

<< Back

EXHIBIT 3

Abbott
A Promise for Life

Print This Page | Back to Web Page

Press Release

Abbott Completes Acquisition of Guidant Vascular Business

Combination of Abbott's and Guidant's Vascular Organizations Creates Leading Vascular Devices Business

Abbott Park, Illinois, April 21, 2006 — Abbott today announced it has completed the acquisition of Guidant's vascular business, which, combined with Abbott's current vascular business, creates one of the leading global vascular devices companies. This acquisition was made in connection with Boston Scientific's acquisition of Guidant Corporation.

"The acquisition of Guidant's vascular business builds on our broad-based business strategy to develop leading positions in attractive health care markets – shaping Abbott for greater balance and strengthening our business mix and breadth of pipeline opportunities," said Miles D. White, chairman and chief executive officer, Abbott.

"The combined Abbott and Guidant business offers a broad line of leading coronary and endovascular products, a pre-eminent sales force, and global manufacturing operations, as well as a state-of-the-art R&D organization, which is developing innovative technologies and devices such as the XIENCE™ V and ZoMaxx™ drug-eluting stents," White said. "Our newly expanded vascular organization has the tools and the talent to transform the way physicians treat vascular disease, impacting the lives of millions of patients around the world."

Broad Vascular Devices Product Portfolio

For the past several years, Abbott has built a competitive vascular business through acquisitions, licensing agreements, and internal scientific and commercial development. With the addition of Guidant's vascular business, Abbott offers physicians, catheterization labs and clinics a complete line of products and technologies for interventional procedures including: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. In addition, the combined business has a broad portfolio of intellectual property, including rapid exchange technology and stent designs, enabling the company to operate effectively in the competitive vascular devices market.

Innovative Research and Development Programs

In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for treating vascular disease. With Guidant, Abbott now has two drug-eluting stents in development: ZoMaxx, a state-of-the-art stent coated with a proprietary immunosuppressant drug, zotarolimus, designed specifically to combat vessel re-narrowing; and XIENCE V, an everolimus-eluting stent on the MULTI-LINK VISION® cobalt chromium stent platform, which recently received approval in Europe. The combined organization also is leading the industry with a number of next-generation research programs including a stent that elutes two drugs targeted at difficult-to-treat patients such as diabetics, and a bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Guidant Vascular Sales and Employees

The transaction provides Abbott with Guidant's vascular intervention and endovascular solutions business units, which had combined sales of more than $1 billion in 2005. These business units add nearly 6,000 employees worldwide to Abbott in three primary locations: Santa Clara, California; Temecula, California; and Clonmel, Ireland. The addition of Guidant's California-based employees boosts Abbott's presence in the state – currently the headquarters of Abbott's diabetes care and vascular businesses – from more than 3,000 to more than 7,000 employees.

Financial Details

Abbott paid $4.1 billion in cash for Guidant's vascular business. In addition, Abbott will pay Boston Scientific milestone payments of $250 million at U.S. Food and Drug Administration approval of Guidant's drug-eluting stent, and an additional payment of $250 million upon a similar approval in Japan. Abbott also provided Boston Scientific with a five-year, $900 million interest-bearing loan. In addition, Abbott has purchased approximately 84 million shares of Boston Scientific stock for $1.4 billion, which represents less than 5 percent of the company.

Abbott expects that the Guidant transaction will be accretive to earnings per share in 2007 and beyond. Further information, including financial details, will be provided on the conference call scheduled for 8 a.m. Central time today (9 a.m. Eastern), as previously announced. A live webcast of the conference call will be accessible through Abbott's Investor Relations Web site at www.abbottinvestor.com. An archived edition of the call will be available after 11 a.m. Central time. Abbott also furnished an 8-K today regarding the Guidant transaction.

About Abbott

Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics. The company now employs 65,000

people and markets its products in more than 130 countries.

Private Securities Litigation Reform Act of 1995 —
A Caution Concerning Forward-Looking Statements
Some statements in this news release may be forward-looking statements for the purposes of the Private Securities Litigation Reform Act of 1995. We caution that these forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated. Economic, competitive, governmental, technological and other factors that may affect Abbott's operations are discussed in the "Risk Factors" section and Exhibit 99.1 of our Securities and Exchange Commission Form 10-K for the period ended December 31, 2005, and are incorporated by reference. We undertake no obligation to release publicly any revisions to forward-looking statements as the result of subsequent events or developments.

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⊞ top of page

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EXHIBIT 4

Abbott
A Promise for Life

Print This Page | Back to Web Page

Abbott Vascular Business Fact Sheet

The combined Abbott and Guidant vascular business offers physicians, catheterization labs and clinics a complete line of products to treat patients with cardiac, vascular and biliary disease. Products and technologies for interventional procedures include: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. Bolstered by the acquisition of Guidant's vascular business in April 2006, Abbott began building its vascular presence with the 1999 acquisition of Perclose, a pioneer in vessel closure technologies. Over the next few years, Abbott strategically assembled a comprehensive vascular devices business through a series of acquisitions, licensing agreements and internal development.

Abbott's Vascular Business -- At a Glance

Worldwide headquarters: San Francisco Bay Area

Web address: www abbottvascular.com

Primary businesses: Coronary, Endovascular and Vessel Closure Devices

Employees: 8,000 (including nearly 6,000 from Guidant)

Facilities: More than 10 commercial, R&D and manufacturing facilities worldwide

Product Portfolio

Abbott offers comprehensive product lines throughout the world in three key areas of focus: coronary, endovascular and vessel closure devices. Key product lines and products include:

Coronary Products:

With Abbott's long history in health care and the advanced medical devices developed by Abbott Vascular and Guidant, the company is uniquely positioned to bring physicians and their patients innovative products for the treatment of coronary artery disease.

Drug-eluting Coronary Stents: The Xience V stent, approved for sale in Europe, is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus.

Bare Metal Coronary Stents: Comprehensive line of bare metal stents designed for a variety of vessel sizes and clinical situations (*Multi-Link Vision* family) The *TriMaxx* bare metal stent is available outside the United States.

Guide Wires: Full lines of coronary guide wires to assist the interventional cardiologist in accessing treatment area (*Hi-Torque* and *Asahi PTCA*)

Catheters: A variety of balloon dilatation catheters and specialty catheters designed to restore blood flow to stenosed arteries (*Tornus* specialty catheter; *Mercury* balloons and *Jography* catheters; *Voyager, CrossSail, PowerSail* and *HighSail*).

Endovascular Products:

Abbott delivers an advanced portfolio of endovascular and biliary products to assist clinicians in a broad range of diagnostic and interventional procedures outside the coronary area (including carotid arteries, renal arteries and bile ducts).

Carotid Stents and Embolic Protection Devices: For the treatment of carotid artery disease. *RX Acculink* is an open-cell, self-expanding nitinol stent available on a rapid exchange delivery system. It is used in conjunction with *RX Accunet* embolic protection device, a polyurethane filter with a nitinol basket. *Xact* is a closed-cell, self-expanding stent used in conjunction with *Emboshield Embolic Protection System*, which features *Barevitre*, a proprietary technology allowing for excellent stent placement.

Biliary stent systems: Broad lines of self-expanding and balloon expanding stents for a variety of applications (*RX Herculink*, *Omnilink* and *Jostent* balloon-expandable stent systems; and the *Absolute*, *Dynalink*, *Xceed* and *Xpert* self-expanding stent systems).

Peripheral Catheters and Guide wires: Full product lines of catheters and guide wires for various vessels and obstructions (*Agilitrac*, *Vietrac*, *Fox PTA*, and *Jocath* catheters; *Hi-Torque* guide wires).

Vessel Closure Products:

A pioneer in vessel closure technologies, Abbott offers products designed to facilitate faster, safer and more secure closure of the vascular access site following catheterizations.

Clip-based closure: The *StarClose Vascular Closure System* delivers a tiny circumferential flexible clip onto the surface of the femoral artery, mechanically closing the access site in the femoral artery securely in a matter of seconds following diagnostic catheterization procedures

Suture-mediated closure: Minimally invasive vessel closure devices that utilize sutures and automate the surgical closure of femoral artery puncture sites following diagnostic or interventional procedures (*Perclose ProGlide*, *Perclose AT* and *Closer S*).

Leading Vascular R&D Program

In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for vascular disease.

Drug-eluting stents

Abbott has two drug-eluting stents in development: *Xience V* and *ZoMaxx*.

- The *Xience V* stent is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus. *Xience V* recently received regulatory approval in Europe and is expected to be launched in the third quarter of 2006. The product is also currently an investigational device in the United States and Japan.
- The *ZoMaxx* stent elutes zotarolimus, a proprietary immunosuppressant drug, and utilizes the *TriMaxx* stent platform, formed from a unique tri-layer composite that allows for thin struts while maintaining optimal visibility via X-ray. *ZoMaxx* is currently in clinical trials in both the United States and internationally, with an expected European launch in 2006.

The company also has a number of next-generation drug-eluting stent programs in development, including:

- A second-generation stent that elutes two drugs (zotarolimus and dexamethasone) intended for difficult-to-treat patients, such as diabetics, where restenosis rates are high.
- A bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Carotid stent clinical trials:

Abbott is a leader in studying carotid stenting as a minimally invasive alternative to surgery for patients with carotid artery disease, a leading cause of stroke. The company is sponsoring/ participating in three clinical trials designed to investigate the benefits of carotid stenting in patients who are at risk of stroke from carotid artery disease.

- ACT I is the first company-sponsored clinical trial to compare carotid artery stenting to carotid artery surgery in asymptomatic patients who normally would be referred for surgery. ACT I utilizes Abbott's *Xact* stent and *Emboshield* embolic protection device.
- CAPTURE 2 is a 10,000-patient post-approval study of high-risk patients using the *RX Acculink* stent and *RX Accunet* embolic protection device.
- Abbott is also participating in the CREST study comparing carotid artery stenting to carotid surgery in normal-risk, symptomatic and asymptomatic patients who normally would be referred for surgery. CREST is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institutes of Health (NIH). CREST utilizes the *RX Acculink* stent and *RX Accunet* embolic protection device.

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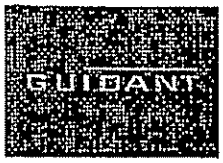
* Trademarks are shown in italics in the text of this fact sheet.

EXHIBIT 5



Print this page

Guidant Enrolls 300 Patients in Drug Eluting Stent Pivotal Trials and Completes Manufacturing Audit

Successful Inspection Brings Company One Step Closer to European Approval; Drug Eluting Stent Milestone Results in Payment to Novartis in Third Quarter

Indianapolis, Ind. — September 21, 2005 — Guidant Corporation (NYSE: GDT) today announced that the company has enrolled more than 300 patients in its SPIRIT II and SPIRIT III clinical trials, meeting a milestone in the company's exclusive license agreement with Novartis Pharma AG.

The company also announced that it has successfully concluded an inspection of its drug eluting stent manufacturing and quality systems at its Temecula site. This inspection was conducted by Guidant's European Notified Body, which is also reviewing the company's submission for approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. The Notified Body found no nonconformities and will recommend certification for Guidant.

"We are pleased with our recent progress with the XIENCE V Everolimus Eluting Coronary Stent System," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant Corporation. "Enrollment in SPIRIT II and SPIRIT III is progressing well, and successful completion of the audit brings us one step closer to approval to market the XIENCE V Coronary Stent System in Europe."

SPIRIT II and SPIRIT III are large-scale pivotal clinical trials evaluating the safety and efficacy of Guidant's drug eluting stent system for the treatment of coronary artery disease. These prospective, randomized, single-blind trials compare XIENCE V, an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium MULTI-LINK VISION® Coronary Stent System platform, versus the TAXUS® Express 2™ Paclitaxel Eluting Coronary Stent System.

Novartis supplies everolimus to Guidant for use in drug eluting stents and provides access to data supporting Guidant filings with regulatory agencies. Under the terms of the agreement with Novartis, the milestone achievement will trigger a $60 million IPR&D charge in the third quarter of 2005, of which $40 million will be paid to Novartis in the third quarter. An additional $20 million will be paid by December 31, 2006.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company, driven by a strong entrepreneurial culture of 12,000 employees, develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

<< Back

EXHIBIT 6

Print this page

Guidant Announces Enrollment of First Patient in FUTURE III Clinical Trial in Europe

Everolimus Eluting Stent Trial Will Provide Additional Safety and Performance Data

Indianapolis, Ind. and Santa Clara, Calif. — April 5, 2004 — Guidant Corporation (NYSE: GDT) today announced that the first patient has been enrolled in FUTURE III, an 800-patient clinical trial that will provide additional safety and performance data to support market launch of Guidant's investigational CHAMPION™ Everolimus Eluting Coronary Stent System outside the United States.

"The initiation of FUTURE III is a significant milestone for Guidant's drug eluting stent program and will provide a deeper understanding of the benefits of everolimus eluting stents for the treatment of coronary artery disease," said Dana G. Mead, Jr., president, Guidant Vascular Intervention. "The start of this new trial demonstrates our confidence in the clinical performance of the CHAMPION Stent System and in our drug eluting stent operational capabilities. We expect that the data from FUTURE III will build upon the excellent results from the FUTURE I and FUTURE II clinical trials, which we anticipate will serve as the clinical basis for regulatory approval in Europe."

FUTURE III is a randomized clinical trial comparing the CHAMPION Everolimus Eluting Coronary Stent System to Guidant's MULTI-LINK ZETA® Coronary Stent System at approximately 90 sites in Europe, the Middle East, Asia, Australia, Canada and New Zealand. The primary endpoint of the trial is in-segment late loss (a measurement of the re-narrowing of the vessel caused by tissue re-growth in the area of the artery in which the stent was placed) at four, six and 12 months following stent implantation.

The trial is designed to show superiority of the CHAMPION Everolimus Eluting Coronary Stent System, which approximately 600 patients will receive, over the MULTI-LINK ZETA Coronary Stent System, which approximately 200 patients will receive. The company expects to present 30-day MACE (major adverse cardiac event) data from the first 120 patients enrolled in FUTURE III before the end of 2004.

Dr. Ulrich Gerckens performed the first implant at the Herzzentrum Siegburg in Germany. Prof. Eberhard Grube, also of the Herzzentrum Siegburg, is the principal investigator of FUTURE III. "The CHAMPION Stent System is a very competitive drug eluting stent system. I look forward to presenting the results from FUTURE III. The study will provide significant data on the use of the bioabsorbable polymer," said Prof. Grube.

Guidant plans to file the third and final module of its submission for Conformité Européenne (CE) Mark approval during the second quarter. The company expects to launch the CHAMPION Everolimus Eluting Coronary Stent System in Europe in the first quarter of 2005, pending regulatory approvals

Guidant's Drug Eluting Stent Program

Guidant has been a global innovator in stent technology since 1995, when its first coronary stent for the treatment of heart disease was launched internationally. Since then, the company has consistently been the market leader in metallic stent sales worldwide. Guidant's drug eluting stent program leverages this market-leading position as well as the company's excellent customer relationships built through its world-class sales force. The company's vascular intervention business is focused on developing broad capabilities in drug eluting stents, including product design, clinical science, polymer science and product commercialization. Guidant holds a worldwide exclusive license from Novartis Pharma AG to use everolimus, a novel proliferation-signal inhibitor with potent anti-proliferative and immunosuppressant properties, in drug eluting stents. Guidant has both durable and bioabsorbable polymer drug carriers in development, providing product design flexibility and potentially offering unique clinical benefits.

Guidant gained immediate entry into the U.S. drug eluting stent market in February through an agreement with Cordis

Corporation, a Johnson & Johnson company. Under the terms of the agreement, Guidant co-promotes Cordis' CYPHER™ Sirolimus-eluting Coronary Stent in the United States. Like everolimus, sirolimus has been shown to prevent cellular proliferation and reduce restenosis.

Guidant's first everolimus eluting stent, the CHAMPION Everolimus Eluting Coronary Stent System, utilizes a bioabsorbable polymer on a stainless steel stent platform with Guidant's MULTI-LINK VISION® Delivery System. Guidant's second everolimus eluting stent, the cobalt chromium MULTI-LINK VISION-based stent system currently being evaluated in the SPIRIT FIRST trial, utilizes a durable polymer.

Guidant's clinical trials employing bioabsorbable polymer technology utilize the FUTURE designation in the study name. The company's clinical trials utilizing durable polymer technology are identified by the SPIRIT designation in the study name.

The FUTURE Clinical Trials

FUTURE I and FUTURE II evaluated safety and performance of an everolimus eluting stent with a bioabsorbable polymer drug carrier and stainless steel stent platform. Results from the FUTURE I and II clinical trials demonstrated safety and efficacy. There was a profound effect in preventing in-stent restenosis (binary angiographic restenosis), with no restenosis at six-month follow-up among patients receiving an everolimus eluting stent (0/46) and an 87 percent reduction of in-stent late loss compared to a metallic stent control.

FUTURE III is an 800-patient clinical trial currently enrolling patients that will provide additional safety and performance data to support market launch of the CHAMPION Everolimus Eluting Stent System outside the United States. Another planned trial, FUTURE IV, is a 975-patient U.S. pivotal trial for the CHAMPION Everolimus Eluting Stent System.

The SPIRIT Clinical Trials

The initial trial in the SPIRIT series, SPIRIT FIRST, enrolled a total of 60 patients at multiple sites in The Netherlands, Denmark and Germany. The primary endpoint of the study is in-stent late loss at six months. Data from the trial will support filings for both a pivotal trial to obtain approval to market the product in the United States and a larger European study to support market launch outside the United States.

Guidant Corporation is a world leader in the treatment of cardiac and vascular disease. The company pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. Driven by a strong entrepreneurial culture of 12,000 employees, Guidant develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

<< Back

EXHIBIT 7

1: Clin Pharmacokinet. 2004;43(2):83-95.

Clinical pharmacokinetics of everolimus.

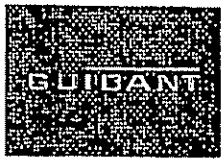
Kirchner GI, Meier-Wiedenbach I, Manns MP.

Department of Gastroenterology, Hepatology and Endocrinology, Zentrum Innere Medizin, Medizinische Hochschule Hannover, Hannover, Germany.
Kirchner.Gabriele@MH-Hannover.de

Everolimus is an immunosuppressive macrolide bearing a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) structure. Everolimus, which has greater polarity than sirolimus, was developed in an attempt to improve the pharmacokinetic characteristics of sirolimus, particularly to increase its oral bioavailability. Everolimus has a mechanism of action similar to that of sirolimus. It blocks growth-driven transduction signals in the T-cell response to alloantigen and thus acts at a later stage than the calcineurin inhibitors ciclosporin and tacrolimus. Everolimus and ciclosporin show synergism in immunosuppression both in vitro and in vivo and therefore the drugs are intended to be given in combination after solid organ transplantation. The synergistic effect allows a dosage reduction that decreases adverse effects. For the quantification of the pharmacokinetics of everolimus, nine different assays using high performance liquid chromatography coupled to an electrospray mass spectrometer, and one enzyme-linked immunosorbent assay, have been developed. Oral everolimus is absorbed rapidly, and reaches peak concentration after 1.3-1.8 hours. Steady state is reached within 7 days, and steady-state peak and trough concentrations, and area under the concentration-time curve (AUC), are proportional to dosage. In adults, everolimus pharmacokinetic characteristics do not differ according to age, weight or sex, but bodyweight-adjusted dosages are necessary in children. The interindividual pharmacokinetic variability of everolimus can be explained by different activities of the drug efflux pump P-glycoprotein and of metabolism by cytochrome P450 (CYP) 3A4, 3A5 and 2C8. The critical role of the CYP3A4 system for everolimus biotransformation leads to drug-drug interactions with other drugs metabolised by this cytochrome system. In patients with hepatic impairment, the apparent clearance of everolimus is significantly lower than in healthy volunteers, and therefore the dosage of everolimus should be reduced by half in these patients. The advantage of everolimus seems to be its lower nephrotoxicity in comparison with the standard immunosuppressants ciclosporin and tacrolimus. Observed adverse effects with everolimus include hypertriglyceridaemia, hypercholesterolaemia, opportunistic infections, thrombocytopenia and leucocytopenia. Because of the variable oral bioavailability and narrow therapeutic index of everolimus, blood concentration monitoring seems to be important. The excellent correlation between steady-state trough concentration and AUC makes the former a simple and reliable index for monitoring everolimus exposure. The target trough concentration of everolimus should range between 3 and 15 microg/L in combination therapy with ciclosporin (trough concentration 100-300 microg/L) and prednisone.

Publication Types:
Review

PMID: 14748618 [PubMed - indexed for MEDLINE]



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Guidant Completes Enrollment in Randomized U.S. Portion of Drug Eluting Stent Pivotal Trial

Large-Scale Trial Evaluating Safety and Efficacy of Next-Generation XIENCE™ V Coronary Stent System

Indianapolis, Ind. and Santa Clara, Calif. — March 15, 2006 — Guidant Corporation (NYSE: GDT) today announced that the company has completed enrollment of 1,002 patients in the randomized U.S. portion of its SPIRIT III drug eluting stent pivotal clinical trial. The randomized U.S. cohort will support Guidant's Premarket Approval submission to the U.S. Food and Drug Administration (FDA) for the company's XIENCE™ V Everolimus Eluting Coronary Stent System for the treatment of coronary artery disease.

SPIRIT III is an international clinical trial consisting of a 1,002-patient prospective, randomized, single-blind U.S. cohort evaluating the safety and efficacy of the XIENCE V Everolimus Eluting Coronary Stent System compared to the TAXUS® Express 2™ Paclitaxel-Eluting Coronary Stent System for the treatment of coronary artery disease, and four non-randomized trial arms. The trial is being conducted in the U.S. and Japan. XIENCE V, which utilizes Guidant's proven MULTI-LINK VISION® cobalt chromium stent platform, received CE Mark approval in January and will be launched in Europe in the second quarter of 2006.

"The completion of enrollment in the randomized U.S. portion of the SPIRIT III trial is a significant milestone for Guidant and demonstrates the commitment of our employees and trial investigators to advancing the science of drug eluting stents," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "We are very pleased with the progress this represents for this next-generation drug eluting stent in the U.S."

Gregg Stone, M.D., Professor of Medicine and Director of Cardiovascular Research & Education of Columbia University Medical Center in New York, and Campbell Rogers, M.D., Director of Cardiac Catheterization at Brigham and Women's Hospital, are co-principal investigators of the study. Dr. Shigeru Saito, Director of Cardiology and Catheterization Laboratories, Shonan Kamakura Hospital, is the principal investigator for the Japan arm of the trial.

"Based on the positive results of SPIRIT FIRST, Guidant's -olimus based XIENCE V Everolimus Eluting Coronary Stent System appears to hold great promise as a next-generation therapy for treating coronary artery disease," said Dr. Rogers. "We look forward to analyzing these data and sharing results of the trial early next year. We also look forward to continuing to examine how the XIENCE stent performs in diverse patient and lesion subsets in upcoming clinical studies."

"We are excited that the SPIRIT III clinical trial has completed enrollment so smoothly and rapidly," said Dr. Stone. "The potential of this highly deliverable XIENCE V Stent System represents a welcome option for physicians caring for patients with coronary artery disease."

In November, Guidant announced that SPIRIT II, a 300-patient, randomized clinical trial evaluating XIENCE V outside the U.S., had completed enrollment in only four months. The single-blind, prospective, randomized, non-inferiority study further evaluates the XIENCE V compared to the TAXUS® Express 2™ Paclitaxel-Eluting Coronary Stent System for the treatment of coronary artery disease.

About XIENCE V

The XIENCE V Everolimus Eluting Coronary Stent System utilizes Guidant's most advanced coronary stent system, the highly deliverable cobalt chromium MULTI-LINK VISION®, which is available on the preferred rapid-exchange platform. Everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation. Guidant is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the

European launch of XIENCE V beginning in the second quarter of 2006.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

This release includes forward-looking statements concerning XIENCE™ V. The statements are based on assumptions about many important factors, including completion of the clinical trial, associated regulatory processes and timelines, and other factors identified on Exhibit 99 to the company's most recent filing on Form 10-Q. Actual results may differ materially. The company does not undertake to update its forward-looking statements.

<<Back

EXHIBIT 10

Print this page

Guidant Reports Excellent 12-Month Results from SPIRIT FIRST Everolimus Eluting Coronary Stent Clinical Trial

Results Demonstrate Sustained Benefit of the XIENCE V Everolimus Eluting Coronary Stent System

Indianapolis, Ind., and Dallas, Texas — November 15, 2005 — Guidant Corporation (NYSE: GDT) today announced 12-month adjudicated results from the company's SPIRIT FIRST clinical trial. SPIRIT FIRST is a prospective, randomized, single-blind trial evaluating Guidant's rapid-exchange XIENCE™ V Everolimus Eluting Coronary Stent System versus an uncoated MULTI-LINK VISION® Coronary Stent System control in de novo (previously untreated) lesions.

"The trial's impressive results demonstrate the sustained efficacy of the XIENCE V Everolimus Eluting Coronary Stent System," said Prof. Patrick W. Serruys, M.D., of the Thoraxcenter, Erasmus University Hospital, Rotterdam, who serves as the study's principal investigator. "The benefit of an everolimus drug eluting stent, with only one device-related MACE event and no thrombotic events, combined with the highly deliverable rapid-exchange VISION stent and stent delivery system, holds great promise for the treatment of patients with cardiovascular disease."

The one-year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control. At one year, the XIENCE V arm demonstrated an angiographic in-stent late loss of 0.23 mm and an in-segment late loss of 0.13 mm, which were 72 percent and 78 percent less, respectively, than the values of the uncoated control (0.81 mm and 0.59 mm). The percent volume obstruction as determined by intravascular ultrasound at one year was 10.7 percent, which was 60 percent less than the control value (26.9 percent).

There were no acute or late stent thromboses reported through the one-year follow-up period. The rate of major adverse cardiac events (MACE) was 15.4 percent (4/26) at one year, compared with 21.4 percent (6/28) for the control. Three of the four MACE events in the treatment arm were not directly related to the XIENCE V Stent, resulting in a device-related MACE rate of 3.8 percent, compared with 21.4 percent for the control. Results were presented today at the American Heart Association Scientific Sessions in Dallas by Prof. Jan J. Piek, M.D. of the Academic Medical Center, Department of Cardiology, University of Amsterdam.

"Everolimus has clearly proven its effectiveness in reducing tissue proliferation in the coronary vessels following stent implantation. We are excited about combining this unique drug with the proven MULTI-LINK VISION, our most advanced coronary stent system, which is available on the rapid-exchange platform physicians prefer," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "We look forward to additional data on this exciting product coming from both SPIRIT II and SPIRIT III. SPIRIT II completed enrollment of 300 patients ahead of schedule last week, and enrollment is proceeding nicely in SPIRIT III as well, with more than 400 patients enrolled to date."

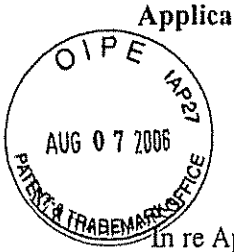
SPIRIT II and SPIRIT III are large-scale pivotal clinical trials evaluating the safety and efficacy of Guidant's drug eluting stent system for the treatment of coronary artery disease. These prospective, randomized, single-blind trials compare XIENCE V, an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium MULTI-LINK VISION Coronary Stent System platform, versus the TAXUS® Express 2™ Paclitaxel Eluting Coronary Stent System.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

<< Back

EXHIBIT H

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **5950**

Application No.: **10/829,074**

Group Art Unit: **3743**

Filing Date: **April 21, 2004**

Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

08/09/2006 HDESTA1 00000001 10829074
04 FC:1464 130.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and

b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074

☐ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 15 to 30 are presently pending. Each of the claims is directed to devices comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating; the devices provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Claim 16 specifies an in-stent late loss in diameter of less than about 0.3 mm, and claims 17 and 18 specify that the stent provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22% or 15%, respectively, as

measured by quantitative coronary angiography. Claims 19 to 22 are similar to claims 15 to 18, but specify mean in-stent late loss and in-stent diameter stenosis values for in a human population. Claims 23 to 30 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty, comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. These methods provide in-stent late loss and/or in-stent diameter stenosis values as recited in claims 15 to 22.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, as recited in claims 15 to 30 on file in this application.

8. Another article published in EuroIntervention in 2005 (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that mean in-stent late loss and diameter stenosis values were 0.24mm and 18%, respectively (*see* abstract), which is within the limits recited in claims 15 to 30 on file in this application.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006

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EXHIBIT 1

Print this page

Guidant Receives European Approval for Drug Eluting Coronary Stent

Company Achieves CE Mark Approval Ahead of Schedule; XIENCE V Launch Slated for Second Quarter

Indianapolis, Ind. and Brussels — January 30, 2006 — Guidant Corporation (NYSE: GDT) today announced that the company has received Conformité Européene (CE) Mark approval for the XIENCE™ V Everolimus Eluting Coronary Stent System. This regulatory certification allows Guidant to begin marketing the drug eluting stent in the 25 countries of the European Union. In addition, the CE Mark Approval is used to support market registrations in other regulated countries including those within Asia, Latin America and Eastern Europe.

"This early approval represents a significant milestone in Guidant's drug eluting stent program and demonstrates our ongoing commitment to advancing the field of cardiovascular therapy through innovative solutions," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "The development of XIENCE V represents years of hard work and dedication by our employees and by trial investigators. We look forward to bringing this next-generation therapy to physicians and patients."

The XIENCE V Everolimus Eluting Coronary Stent System utilizes Guidant's most advanced coronary stent system, the highly deliverable cobalt chromium MULTI-LINK VISION®, which is available on the preferred rapid-exchange platform. Everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation.

"Completion of the CE Mark approval process for XIENCE V follows on the heels of impressive clinical results from the SPIRIT FIRST trial, which demonstrated the benefits of an everolimus drug eluting stent," said Prof. Patrick W. Serruys, M.D., of the Thoraxcenter, Erasmus University Hospital, Rotterdam, who served as the study's principal investigator. "With this approval, physicians in Europe will have an excellent treatment option for patients requiring a drug eluting stent."

Guidant is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE V beginning in the second quarter of 2006.

In November, Guidant announced completion of enrollment in only four months of SPIRIT II, a 300-patient, randomized clinical trial evaluating XIENCE V. The single-blind, prospective, randomized, non-inferiority study further evaluates the XIENCE V compared to the TAXUS® Express 2™ Paclitaxel-eluting coronary stent system for the treatment of coronary artery disease.

Guidant's 1,380-patient SPIRIT III global clinical trial is evaluating the XIENCE V Stent System in the United States and Japan. The randomized U.S. cohort, which will support U.S. Premarket Approval submission, has enrolled more than 70 percent of the required patients and is expected to complete enrollment later this quarter.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

This release includes forward-looking statements concerning XIENCE V. The statements are based on assumptions about many important factors, including satisfactory enrollment and completion of the clinical trial, associated regulatory processes and timelines, and other factors identified on Exhibit 99 to the company's most recent filing on Form 10-Q. Actual results may differ materially. The company does not undertake to update its forward-looking statements.

<< Back

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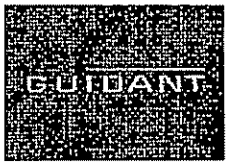

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Guidant Provides Update

Indianapolis, Ind. — October 19, 2005 — Guidant Corporation (NYSE: GDT), a world leader in the treatment of cardiac and vascular disease, today responded to statements by Johnson & Johnson on its pending acquisition of the Company and provided an update on its two major businesses.

Transaction Update

In response to Johnson & Johnson's comments yesterday, Ronald W. Dollens, president and CEO of Guidant Corporation, stated, "While neither company depends on this transaction for its continued future success, Guidant believes that the strategic rationale for combining the two companies is as strong today as when we entered into the Merger Agreement." Guidant anticipates that the pending transaction will receive FTC clearance in October. The Company does not expect to make any specific comments on the pending transaction until after FTC approval.

Business Performance

"Guidant's third quarter results will reflect the temporary unavailability of the CONTAK RENEWAL 3 and 4 family of heart failure devices during the full month of July and part of August, partially offset by sequential growth of U.S. coronary stent revenue, and continuing sales growth of our emerging businesses," Dollens reported. "At the end of the quarter, data suggest our implantable defibrillator implant rate exceeded 80 percent of the pre-product notification level and is over 100 percent of the rate one year ago."

Dollens continued, "As previously announced, Guidant is launching several recently approved cardiac rhythm management systems during the fourth quarter, including the revolutionary Latitude Patient Management system. Physicians are expressing enthusiasm for the new wireless capability to monitor patients, improve their compliance, and monitor device status independent of patient effort." Dollens further observed, "Our drug eluting stent development program continues to make important progress toward European launch during the first half of next year. We are expanding manufacturing capacity, increasing productivity, and recently received FDA approval to expand clinical trial enrollment."

"While recent events and the publicity surrounding them will impact our short-term results, we believe that the fundamentals of our business and the markets that we serve remain strong and our outlook is positive," Dollens noted. "Our track record of success over the years has been driven in large part by the dedication of our people to the needs of patients and physicians who use our products. We continue to be committed to providing the highest quality products for patients who critically need them and we are confident that the value of the Company remains strong."

Cardiac Rhythm Management Products Update

Consistent with an anticipated new product cycle, several significant new products were approved (cleared) by FDA during the third quarter. They include:

- VITALITY HE implantable defibrillator; Guidant's first high-energy product to offer the advanced functionality of the VITALITY family.
- CONTAK RENEWAL 3 RF cardiac resynchronization-defibrillator; this is Guidant's first wireless and wandless CRT-D and is designed to enhance the speed and convenience of patient care.
- ZOOM LATITUDE programmer; this next generation programmer is designed to interface with devices that include remote monitoring capability.

- LATITUDE Communicator and secure data storage system; these elements represent the final components of the Latitude Patient Management system.

Actions taken by the Company during the quarter reflect Guidant's commitment to provide more timely information to physicians and patients about our devices. Our products continue to demonstrate high performance and reliability, and tens of thousands of people are alive today and hundreds of thousands feel better as a result of Guidant's technologies. Guidant will continue to focus on meeting and exceeding the expectations of physicians, patients and the FDA.

Drug Eluting Stent Progress

Guidant announced today that its drug eluting stent development program continues to demonstrate progress and the Company has enrolled more than 500 patients in the SPIRIT II and III clinical trials since June. SPIRIT III is a large-scale pivotal clinical trial evaluating XIENCE™ V, an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium rapid-exchange MULTI-LINK VISION® RX Coronary Stent System platform. Guidant plans to use the results of the SPIRIT III trial to obtain FDA approval for XIENCE V for the treatment of coronary artery disease. Results of the SPIRIT II study will provide additional clinical data to support the launch of XIENCE V in Europe and several countries outside the United States.

Earlier in the quarter, Guidant announced attainment of an enrollment milestone in the Company's exclusive license agreement with Novartis Pharma AG. Novartis supplies everolimus to Guidant for use in drug eluting stents and provides access to data supporting Guidant filings with regulatory agencies.

In addition, the Company plans to present one-year follow up data from SPIRIT I at the American Heart Association meeting in November 2005. SPIRIT I is a prospective, randomized, single-blind pilot study evaluating XIENCE V versus an uncoated MULTI-LINK VISION Coronary Stent System control in de novo (previously untreated) lesions.

During the quarter, the Company also announced that it successfully concluded an inspection of its drug eluting stent manufacturing and quality systems at its Temecula site. This inspection was conducted by Guidant's European Notified Body, which is also reviewing the Company's submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. The Notified Body found no nonconformities and will recommend certification for Guidant's manufacturing facility.

Guidant Corporation

Guidant Corporation pioneers lifesaving technology, giving an opportunity for a better life today to millions of cardiac and vascular patients worldwide. The Company, driven by a strong entrepreneurial culture of more than 12,000 employees, develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information, visit www.guidant.com.

This release includes forward-looking statements that are based on assumptions about many important factors, including market trends and competition, particularly in connection with expanded indications and reimbursement for cardiac rhythm management products; satisfactory clinical and regulatory progress; progress with respect to the merger, including satisfaction of conditions to closing, including antitrust approvals; economic conditions, including exchange rates; litigation developments; and the factors listed on exhibit 99 to Guidant's most recent 10-Q. As such, they involve risks that could cause actual results to differ materially. The company does not undertake to update its forward-looking statements.

ABBOTT COMPLETES ACQUISITION OF GUIDANT VASCULAR BUSINESS

—COMBINATION OF ABBOTT'S AND GUIDANT'S VASCULAR ORGANIZATIONS CREATES LEADING VASCULAR DEVICES BUSINESS —

Abbott Park, Illinois, April 21, 2006 — Abbott today announced it has completed the acquisition of Guidant's vascular business, which, combined with Abbott's current vascular business, creates one of the leading global vascular devices companies. This acquisition was made in connection with Boston Scientific's acquisition of Guidant Corporation.

"The acquisition of Guidant's vascular business builds on our broad-based business strategy to develop leading positions in attractive health care markets - shaping Abbott for greater balance and strengthening our business mix and breadth of pipeline opportunities," said Miles D. White, chairman and chief executive officer, Abbott.

"The combined Abbott and Guidant business offers a broad line of leading coronary and endovascular products, a pre-eminent sales force, and global manufacturing operations, as well as a state-of-the-art R&D organization, which is developing innovative technologies and devices such as the XIENCE™ V and ZoMaxx™ drug-eluting stents," White said. "Our newly expanded vascular organization has the tools and the talent to transform the way physicians treat vascular disease, impacting the lives of millions of patients around the world."

Broad Vascular Devices Product Portfolio
For the past several years, Abbott has built a competitive vascular business through acquisitions, licensing agreements, and internal scientific and commercial development. With the addition of Guidant's vascular business, Abbott offers physicians, catheterization labs and clinics a complete line of products and technologies for interventional procedures including: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. In addition, the combined business has a broad portfolio of intellectual property, including rapid exchange technology and stent designs, enabling the company to operate effectively in the competitive vascular devices market.

Innovative Research and Development Programs
In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for treating vascular disease. With Guidant, Abbott now has two drug-eluting stents in development: ZoMaxx, a state-of-the-art stent coated with a proprietary immunosuppressant drug, zotarolimus, designed specifically to combat vessel re-narrowing; and XIENCE V, an everolimus-eluting stent on the MULTI-LINK VISION® cobalt chromium stent platform, which recently received approval in Europe. The combined organization also is leading the industry with a number of next-generation research programs including a stent that elutes two drugs targeted at difficult-to-treat patients such as diabetics, and a bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Guidant Vascular Sales and Employees
The transaction provides Abbott with Guidant's vascular intervention and endovascular solutions business units, which had combined sales of more than $1 billion in 2005. These business units add nearly 6,000 employees worldwide to Abbott in three primary locations: Santa Clara, California; Temecula, California; and Clonmel, Ireland. The addition of Guidant's California-based employees boosts Abbott's presence in the state - currently the headquarters

of Abbott's diabetes care and vascular businesses – from more than 3,000 to more than 7,000 employees.

Financial Details
Abbott paid $4.1 billion in cash for Guidant's vascular business. In addition, Abbott will pay Boston Scientific milestone payments of $250 million at U.S. Food and Drug Administration approval of Guidant's drug-eluting stent, and an additional payment of $250 million upon a similar approval in Japan. Abbott also provided Boston Scientific with a five-year, $900 million interest-bearing loan. In addition, Abbott has purchased approximately 64 million shares of Boston Scientific stock for $1.4 billion, which represents less than 5 percent of the company.

Abbott expects that the Guidant transaction will be accretive to earnings per share in 2007 and beyond. Further information, including financial details, will be provided on the conference call scheduled for 8 a.m. Central time today (9 a.m. Eastern), as previously announced. A live webcast of the conference call will be accessible through Abbott's Investor Relations Web site at www.abbottinvestor.com. An archived edition of the call will be available after 11 a.m. Central time. Abbott also furnished an 8-K today regarding the Guidant transaction.

About Abbott
Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics. The company now employs 65,000 people and markets its products in more than 130 countries.

Private Securities Litigation Reform Act of 1995 —
A Caution Concerning Forward-Looking Statements
Some statements in this news release may be forward-looking statements for the purposes of the Private Securities Litigation Reform Act of 1995. We caution that these forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated. Economic, competitive, governmental, technological and other factors that may affect Abbott's operations are discussed in the "Risk Factors" section and Exhibit 99.1 of our Securities and Exchange Commission Form 10-K for the period ended December 31, 2005, and are incorporated by reference. We undertake no obligation to release publicly any revisions to forward-looking statements as the result of subsequent events or developments.

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Back to Top

EXHIBIT 4

Abbott
A Promise for Life

Abbott's Vascular Business
Fact Sheet

The combined Abbott and Guidant vascular business offers physicians, catheterization labs and clinics a complete line of products to treat patients with cardiac, vascular and biliary disease. Products and technologies for interventional procedures include: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. Bolstered by the acquisition of Guidant's vascular business in April 2006, Abbott began building its vascular presence with the 1999 acquisition of Perclose, a pioneer in vessel closure technologies. Over the next few years, Abbott strategically assembled a comprehensive vascular devices business through a series of acquisitions, licensing agreements and internal development.

Abbott's Vascular Business – At a Glance

Worldwide headquarters:	San Francisco Bay Area
Web address:	www.abbottvascular.com
Primary businesses:	Coronary, Endovascular and Vessel Closure Devices
Employees:	8,000 (including nearly 6,000 from Guidant)
Facilities:	More than 10 commercial, R&D and manufacturing facilities worldwide

Product Portfolio

Abbott offers comprehensive product lines throughout the world in three key areas of focus: coronary, endovascular and vessel closure devices. Key product lines and products include:

Coronary Products:

With Abbott's long history in health care and the advanced medical devices developed by Abbott Vascular and Guidant, the company is uniquely positioned to bring physicians and their patients innovative products for the treatment of coronary artery disease.

Drug-eluting Coronary Stents: The *Xience V* stent, approved for sale in Europe, is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus.

Bare Metal Coronary Stents: Comprehensive line of bare metal stents designed for a variety of vessel sizes and clinical situations (*Multi-Link Vision* family). The *TriMaxx* bare metal stent is available outside the United States.

Guide Wires: Full lines of coronary guide wires to assist the interventional cardiologist in accessing treatment area (*Hi-Torque* and *Asahi PTCA*).

Catheters: A variety of balloon dilatation catheters and specialty catheters designed to restore blood flow to stenosed arteries (*Tornus* specialty catheter; *Mercury* balloons and *Jography* catheters; *Voyager*, *CrossSail*, *PowerSail* and *HighSail*).

Endovascular Products:
Abbott delivers an advanced portfolio of endovascular and biliary products to assist clinicians in a broad range of diagnostic and interventional procedures outside the coronary area (including carotid arteries, renal arteries and bile ducts).

Carotid Stents and Embolic Protection Devices: For the treatment of carotid artery disease. *RX Acculink* is an open-cell, self-expanding nitinol stent available on a rapid exchange delivery system. It is used in conjunction with *RX Accunet* embolic protection device, a polyurethane filter with a nitinol basket. *Xact* is a closed-cell, self-expanding stent used in conjunction with *Emboshield Embolic Protection System*, which features *Barewire*, a proprietary technology allowing for excellent stent placement.

Biliary stent systems: Broad lines of self-expanding and balloon expanding stents for a variety of applications (*RX Herculink*, *Omnilink* and *Jostent* balloon-expandable stent systems; and the *Absolute*, *Dynalink*, *Xceed* and *Xpert* self-expanding stent systems).

Peripheral Catheters and Guide wires: Full product lines of catheters and guide wires for various vessels and obstructions (*Agiltrac*, *Viatrac*, *Fox PTA*, and *Jocath* catheters; *Hi-Torque* guide wires).

Vessel Closure Products:
A pioneer in vessel closure technologies, Abbott offers products designed to facilitate faster, safer and more secure closure of the vascular access site following catheterizations.

Clip-based closure: The *StarClose Vascular Closure System* delivers a tiny circumferential flexible clip onto the surface of the femoral artery, mechanically closing the access site in the femoral artery securely in a matter of seconds following diagnostic catheterization procedures.

Suture-mediated closure: Minimally invasive vessel closure devices that utilize sutures and automate the surgical closure of femoral artery puncture sites following diagnostic or interventional procedures (*Perclose ProGlide*, *Perclose AT* and *Closer S*).

Leading Vascular R&D Program
In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for vascular disease.

Drug-eluting stents
Abbott has two drug-eluting stents in development: *Xience V* and *ZoMaxx*.

- The *Xience V* stent is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus. *Xience V* recently received regulatory approval in Europe and is expected to be launched in the third quarter of 2006. The product is also currently an investigational device in the United States and Japan.

- The *ZoMaxx* stent elutes zotarolimus, a proprietary immunosuppressant drug, and utilizes the *TriMaxx* stent platform, formed from a unique tri-layer composite that allows for thin struts while maintaining optimal visibility via X-ray. *ZoMaxx* is currently in clinical trials in both the United States and internationally, with an expected European launch in 2006.

The company also has a number of next-generation drug-eluting stent programs in development, including:

- A second-generation stent that elutes two drugs (zotarolimus and dexamethasone) intended for difficult-to-treat patients, such as diabetics, where restenosis rates are high.
- A bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Carotid stent clinical trials:

Abbott is a leader in studying carotid stenting as a minimally invasive alternative to surgery for patients with carotid artery disease, a leading cause of stroke. The company is sponsoring/ participating in three clinical trials designed to investigate the benefits of carotid stenting in patients who are at risk of stroke from carotid artery disease.

- ACT I is the first company-sponsored clinical trial to compare carotid artery stenting to carotid artery surgery in asymptomatic patients who normally would be referred for surgery. ACT I utilizes Abbott's *Xact* stent and *Emboshield* embolic protection device.
- CAPTURE 2 is a 10,000-patient post-approval study of high-risk patients using the *RX Acculink* stent and *RX Accunet* embolic protection device.
- Abbott is also participating in the CREST study comparing carotid artery stenting to carotid surgery in normal-risk, symptomatic and asymptomatic patients who normally would be referred for surgery. CREST is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institutes of Health (NIH). CREST utilizes the *RX Acculink* stent and *RX Accunet* embolic protection device.

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* Trademarks are shown in italics in the text of this fact sheet.

1: Clin Pharmacokinet. 2004;43(2):83-95.

Clinical pharmacokinetics of everolimus.

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Everolimus is an immunosuppressive macrolide bearing a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) structure. Everolimus, which has greater polarity than sirolimus, was developed in an attempt to improve the pharmacokinetic characteristics of sirolimus, particularly to increase its oral bioavailability. Everolimus has a mechanism of action similar to that of sirolimus. It blocks growth-driven transduction signals in the T-cell response to alloantigen and thus acts at a later stage than the calcineurin inhibitors ciclosporin and tacrolimus. Everolimus and ciclosporin show synergism in immunosuppression both in vitro and in vivo and therefore the drugs are intended to be given in combination after solid organ transplantation. The synergistic effect allows a dosage reduction that decreases adverse effects. For the quantification of the pharmacokinetics of everolimus, nine different assays using high performance liquid chromatography coupled to an electrospray mass spectrometer, and one enzyme-linked immunosorbent assay, have been developed. Oral everolimus is absorbed rapidly, and reaches peak concentration after 1.3-1.8 hours. Steady state is reached within 7 days, and steady-state peak and trough concentrations, and area under the concentration-time curve (AUC), are proportional to dosage. In adults, everolimus pharmacokinetic characteristics do not differ according to age, weight or sex, but bodyweight-adjusted dosages are necessary in children. The interindividual pharmacokinetic variability of everolimus can be explained by different activities of the drug efflux pump P-glycoprotein and of metabolism by cytochrome P450 (CYP) 3A4, 3A5 and 2C8. The critical role of the CYP3A4 system for everolimus biotransformation leads to drug-drug interactions with other drugs metabolised by this cytochrome system. In patients with hepatic impairment, the apparent clearance of everolimus is significantly lower than in healthy volunteers, and therefore the dosage of everolimus should be reduced by half in these patients. The advantage of everolimus seems to be its lower nephrotoxicity in comparison with the standard immunosuppressants ciclosporin and tacrolimus. Observed adverse effects with everolimus include hypertriglyceridaemia, hypercholesterolaemia, opportunistic infections, thrombocytopenia and leucocytopenia. Because of the variable oral bioavailability and narrow therapeutic index of everolimus, blood concentration monitoring seems to be important. The excellent correlation between steady-state trough concentration and AUC makes the former a simple and reliable index for monitoring everolimus exposure. The target trough concentration of everolimus should range between 3 and 15 microg/L in combination therapy with ciclosporin (trough concentration 100-300 microg/L) and prednisone.

Publication Types:
Review

PMID: 14748618 [PubMed - indexed for MEDLINE]

EXHIBIT 7

A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial

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Conflict of interest: All authors declare no conflict of interest.

KEYWORDS

Stent, eluting stent, everolimus, randomized trial

Abstract

Background: Everolimus is a sirolimus analogue with similar efficacy in animal models, and has been previously successfully tested in humans using an erodable polymer.

Methods: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus eluting from a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Sixty patients were allocated to stent implantation with an everolimus-eluting stent (n=28) or an identical bare stent (n=32). Patients had either stable, unstable angina or silent ischaemia. Suitable lesions treated were single *de novo* native coronary lesions with 50-99% stenosis and could be covered by a 18 mm stent. The primary endpoint was in-stent late loss at 180 days, analysed on a per treatment basis. The major secondary endpoint was percent in-stent volume obstruction (%VO) as measured by intravascular ultrasound (IVUS) at 180 days. The clinical secondary endpoint was major adverse cardiac events (MACE) at 180 days.

Results: At 6 months, (matched pairs angiographic analysis), the in-stent late loss, percentage diameter stenosis and percentage of patients with binary restenosis were 0.10 mm, 16% and 0% respectively, in the everolimus arm (n=23), as compared with 0.87 mm, 39% and 25.9%, respectively in the bare stent arm (n=27, p<0.001 for late loss and diameter stenosis, p = 0.01 for restenosis). Significantly less neointimal hyperplasia was observed in the everolimus group compared to the bare stent group (10 ± 13 mm^3 vs 38 ± 19 mm^3, p<0.001) and similarly, less volume obstruction (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). A major adverse cardiac event occurred in 2 patients in the everolimus arm versus 6 in the bare stent arm.

Conclusion: Everolimus eluted from a durable polymer on a cobalt chromium stent effectively suppresses neointimal growth at 6 months compared to an identical bare stent.

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Funding sources: This study was sponsored by Guidant Corporation.

Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia[1,2].

Everolimus is an effective anti-proliferative agent[3]. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of mammalian Target Of Rapamycin (mTOR), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with its function. Disabling mTOR explains the cell cycle arrest at the late G1 stage caused by everolimus and sirolimus.

The feasibility of using everolimus on a drug eluting stent was determined by the FUTURE I trial[4]. This trial utilized an S-stent and bioabsorbable polymer system (both Biosensors International, Singapore) and confirmed the safety of the everolimus-eluting stent at 6 and 12 months. At 6 months, a 7.7% Major Adverse Cardiac Event (MACE) rate was observed with no thrombosis and no late incomplete apposition. The efficacy was demonstrated by significant reduction of in-stent tissue proliferation at 6 months: both angiographic in-stent late loss and IVUS% neointimal volume were reduced by 87%. No angiographic in-stent binary restenosis was observed in the everolimus-eluting stent arm. The 12 month FUTURE I results showed sustained safety and efficacy with no new MACE events, no aneurysms, no late stent malapposition, and no thrombosis observed between 6 and 12 months. Minimal Lumen Area and Luminal Volume Index were maintained up to 12 months and no in-stent binary restenosis was observed up to 12 months.

The SPIRIT First clinical trial represents the first clinical evaluation of the Guidant XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE™ V Everolimus Eluting CSS), to investigate the potential benefits of the local application of everolimus in a durable polymer in combination with a thin strut cobalt chromium stent.

Methods

Patient selection

This randomized single-blind trial was performed at 9 medical centers and enrolled patients from December 2003 to April 2004. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were aged above 18 years and had received a diagnosis of stable or unstable angina or silent ischaemia. Additional eligibility criteria were the presence of a single primary *de novo* coronary lesion that was 3.0 mm in diameter as assessed by on-line QCA, that could be covered by an 18 mm stent, a stenosis of between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of an unprotected left main coronary artery, an ostial location, located within 2 mm of a bifurcation, a lesion with moderate to heavy calcification, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, chromium, nickel, tungsten, everolimus, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated.

The Everolimus-eluting stent

The Guidant XIENCE™ V Everolimus Eluting CSS is comprised of the Guidant MULTI-LINK VISION® Stent and delivery system, and a drug eluting coating. The Guidant MULTI-LINK VISION® Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a nonerodable polymer (this drug layer was coated over another nonerodable polymer primer layer). This coating includes of acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimeter of stent surface area with no top coat polymer layer. The stent is designed to release approximately 70% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation[5]. Everolimus has received market approval in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria and prior to the procedure, patients were allocated through a telephone randomization service and assigned in a 1:1 ratio to either an everolimus eluting stent or bare metal stent. A single stent 3.0 mm in diameter, 18 mm long was used in the study.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the rated burst pressure. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was allowed with a balloon shorter than the implanted stent. In the event of a dissection occurring at the edge of the implanted stent, it was recommended that a single additional bare Guidant MULTI-LINK VISION® stent be implanted as animal data only on single everolimus stent implantation were available at the onset of the study; these patients were *a priori* excluded from the per-treatment analysis but are part of the acute success population. IVUS was performed after angiographically optimal stent placement had been obtained and was repeated if additional post-dilatation was performed.

Intravenous boluses of heparin were administered according to local standard practice. Treatment with aspirin, at a minimum dose of 80 mg per day, was started at least 24 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 24 hours before the procedure, followed

by 75 mg daily for three months. Treatment with ticlopidine was permitted in case of clopidogrel hypersensitivity. Device success was defined as a final in-stent diameter stenosis of less than 50 percent by QCA using the assigned device. Clinical success was defined as the successful implantation of any device, with stenosis of less than 50 percent of the vessel diameter by QCA and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and 6 months. Further evaluations will be performed at 9 months and 1 year, with annual evaluations out to 5 years. At outpatient visits, patients were asked specific questions about the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. They were also monitored for MACE. Angiographic and IVUS evaluations were performed at 6 months, and will be repeated at 1 year. Prior to performing a follow-up angiogram, the physician was required to record in the source documents whether a revascularization (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: computer-defined Minimal Luminal Diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis ≥50% at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as matched pairs in the manuscript and as unmatched pairs in the Appendix. Unmatched pairs data is most commonly presented and utilises the mean QCA results of all projections obtained. Matched pairs data is more accurate as it compares the same views post-procedure and at follow-up and uses only QCA data of identical projections.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array intravascular ultrasound using automated pullback at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm. The Stent Volume (SV) and Lumen Volume (LV) were calculated according to Simpson's rule. The intra-stent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intra-stent neointimal volume/stent volume*100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[6]. Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.

Study endpoints

The primary angiographic endpoint was in-stent luminal late loss, as determined by quantitative angiography. Secondary endpoints (QCA and IVUS) at 6 months and 1 year included the in-stent and in-segment late loss, angiographic binary restenosis rate, percentage diameter stenosis; and in-stent percentage volume obstruction. In-stent was defined as within the margins of the stent while in-segment was defined as located either within the margins of the stent or 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the follow-up and post-procedure minimum luminal diameter. Secondary clinical endpoints were a composite of major cardiac events, including cardiac death, Q-wave or non-Q-wave myocardial infarction, clinically driven surgical or percutaneous revascularization of the target lesion (MACE) or vessel (Target Vessel Failure) at 30 days, 6 months, 9 months, and annually up to 5 years after the index procedure; and acute device, procedure and clinical success. All deaths that could not be clearly attributed to another cause were considered cardiac deaths. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase-MB, in the absence of new Q waves on electrocardiography.

The endpoints were adjudicated by an independent clinical events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population which consisted of patients who had no bailout stenting and no major protocol deviations, as evaluated in a blinded manner. Acute success was analyzed on the entire patient population.

The sample size for the study was determined based on the primary endpoint of in-stent late loss at 180 days and on the following assumptions: a single comparison of active to uncoated; one-tailed t-test, unequal and unknown variances in the two groups being compared; α=0.05; true mean difference between the bare stent group and the treatment group of 0.48 mm. This assumption was made based on the results of the VISION Registry (mean late loss=0.83 mm)[7], SIRIUS trial (mean late loss=0.17 mm)[8] and TAXUS IV trial (mean late loss=0.39 mm)[9]. (Assume the true mean late loss for the treatment group is 0.35 mm, the difference between the bare stent group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm). The standard deviation was assumed to be 0.56 mm in the bare stent group and 0.38 mm in the treatment group (based on the results of the VISION Registry study and SIRIUS trial); approximately 20% rate of lost to follow-up or dropout; approximate-

ly 10% of patients with bailout stents. Given the above assumptions, 30 patients per arm (with the analysis of 22 evaluable patients per arm) will provide 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) would provide more than 96% power.

Binary variables were compared using Fisher's Exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon Rank-Sum test, except for the primary endpoint which was evaluated with a one sided *t*-test. Final 6-month results are presented in the manuscript, while the Appendix contains results that were available at the time that the 180-day report was prepared.

Results

Patient characteristics

Between December 2003 and April 2004, 28 patients were randomly assigned to receive the everolimus-eluting stent, and 32 were assigned to receive the bare stent. As defined in the protocol, all results (except acute success) are presented for the per-treatment population (27 patients in the everolimus group, and 29 patients in the bare stent group, Figure 1). In the everolimus group there was one bailout procedure, and in the bare stent group there were two bailout procedures and one major protocol deviation (the patient was on the heart transplant waiting list). With the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus group, the two groups were similar with respect to clinical variables examined (Table 1).

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus stent (n=27)	Bare stent (n=29)	All patients (n=56)
Age(yrs)	64 ± 10	61 ± 9	63 ± 9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring medication (%)	70	41	55
Hyperlipidemia requiring medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left anterior descending	48	45	46
Left circumflex	22	21	21
RCA	30	34	32
AHA / ACC Lesion Class (%)**			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference Vessel Diameter (mm ± SD)	2.61 ± 0.40	2.71 ± 0.28	2.66 ± 0.34
Lesion length (mm ± SD)	10.1 ± 2.6	10.9 ± 3.3	10.5 ± 3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

** AHA / ACC = American Heart Association / American College of Cardiology

FIGURE 1

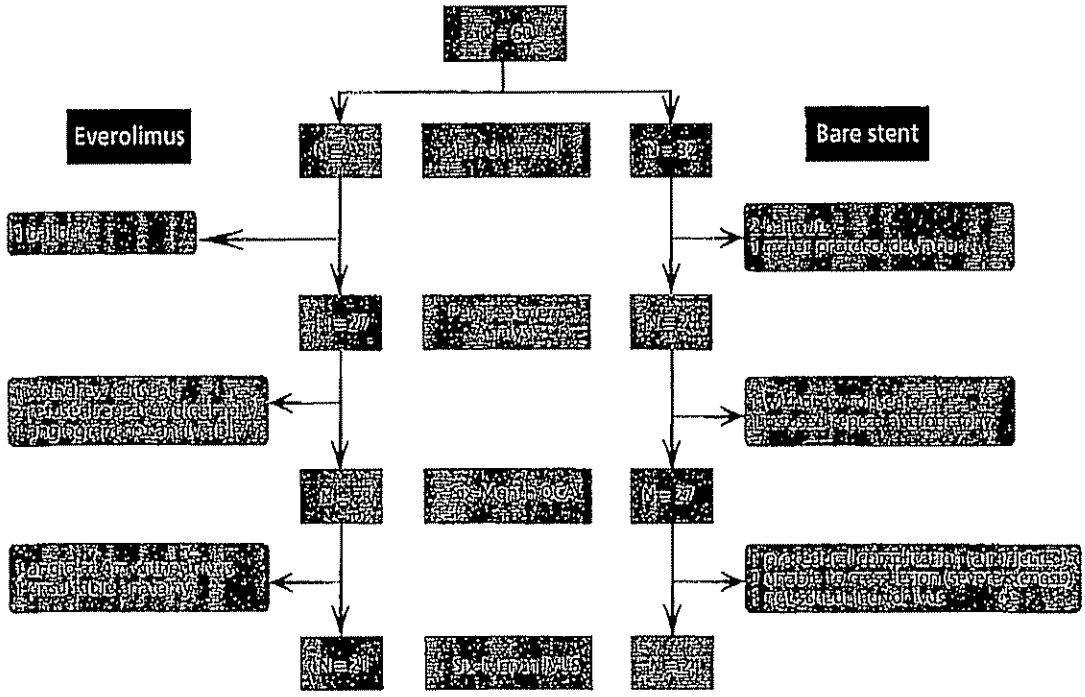

Fig. 1: Flowchart of patients

Procedural characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Glycoprotein IIb/IIIa inhibitors, used at the investigators' discretion, were administered to 7.4% of the patients in the everolimus group and 3.4% of those in the bare stent group. The two groups did not differ significantly with respect to the rate of device success (96.4% in the everolimus group and 93.8% in the bare stent group) or clinical success (95.4% in the everolimus group and 100% in the bare stent group).

Quantitative coronary angiography analysis

Angiographic data at 6 months were available for 50 of the 56 analysable patients (89.3%). The mean reference diameter of the target vessel, the mean length of the lesion at baseline, the reference vessel diameter and mean MLD of the stented segment were similar in the two groups (Tables 1 and 2). At six months, with matched pairs analysis, the mean MLD of the stented segment was significantly greater in the everolimus group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were 0.10 mm, 16%, and 0%, respectively, in the everolimus group, as compared with 0.87 mm, 39%, and 25.9%, respectively, in the bare stent group ($p<0.001$ for late loss and diameter stenosis, $p=0.01$ for restenosis). Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 and Figure 3 show the results of sub-segmental quantitative angiographic analyses for matched pairs. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus group than in the bare stent group ($p<0.01$ for proximal and $p=0.04$ for distal). The late luminal loss in the stented segment was significantly less in the everolimus group than in the bare stent group ($p \leq 0.001$).

Intravascular ultrasound evaluation

At six months follow-up, intravascular ultrasound evaluation showed no significant differences between the two groups with respect to the volume of the stent or the vessel volume (Table 3). Significantly

FIGURE 2

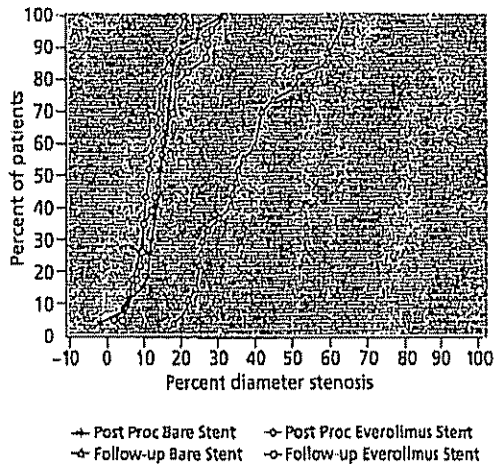

Fig. 2: Cumulative frequency of stenosis (in-stent) immediately after stenting and at six months

FIGURE 3

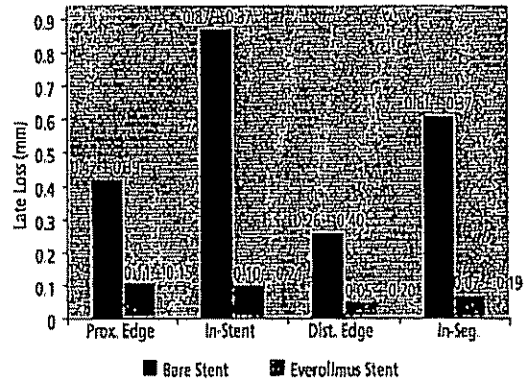

Fig. 3: Comparison of in-segment / in-stent late loss

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Matched Pairs).

	Proximal Edge			In-Stent			Distal Edge			In-Segment Analysis		
	Everolimus (n=23)	Bare (n=27)	p-value	Everolimus (n=23)	Bare (n=27)	p-value	Everolimus (n=23)	Bare (n=27)	p-value	Everolimus (n=23)	Bare (n=27)	p-value
Reference Vessel Diameter (mm)												
After procedure	2.80 ± 0.33	3.04 ± 0.38	0.06*	2.71 ± 0.28	2.89 ± 0.35	0.11*	2.64 ± 0.30	2.80 ± 0.39	0.21*	2.65 ± 0.30	2.84 ± 0.41	0.10*
At 6 months	2.78 ± 0.32	2.67 ± 0.40	0.22*	2.70 ± 0.31	2.58 ± 0.37	0.25*	2.61 ± 0.37	2.46 ± 0.36	0.19*	2.61 ± 0.36	2.59 ± 0.36	0.89*
Minimal Luminal Diameter (mm)												
After procedure	2.56 ± 0.44	2.61 ± 0.45	0.79*	2.38 ± 0.25	2.45 ± 0.31	0.50*	2.23 ± 0.41	2.26 ± 0.45	0.77*	2.11 ± 0.35	2.14 ± 0.40	1.00*
At 6 months	2.45 ± 0.46	2.19 ± 0.49	0.04*	2.28 ± 0.33	1.58 ± 0.41	< 0.001*	2.18 ± 0.38	2.00 ± 0.45	0.21*	2.04 ± 0.40	1.54 ± 0.41	< 0.001*
Late Loss (mm)	0.11 ± 0.15	0.42 ± 0.39	<0.01*	0.10 ± 0.21	0.87 ± 0.37	< 0.001***	0.05 ± 0.20	0.26 ± 0.40	0.04*	0.07 ± 0.19	0.61 ± 0.37	< 0.001*
Diameter Stenosis (%DS)												
After procedure	9 ± 11	14 ± 9	0.07*	12 ± 5	15 ± 6	0.05*	16 ± 10	20 ± 10	0.16*	20 ± 8	24 ± 9	0.05*
At 6 months	12 ± 12	17 ± 17	0.26*	16 ± 8	39 ± 14	< 0.001*	16 ± 10	19 ± 14	0.82*	22 ± 11	41 ± 14	< 0.001*
Binary Restenosis Rates	4.3%	3.7%	1.00**	0.0%	25.9%	0.01**	0.0%	7.4%	0.49**	4.3%	33.3%	0.01**

* two-sided Wilcoxon rank sum test ** two-sided Fisher's Exact test *** One-sided t-test † Fisher's Exact test

Table 3. IVUS measurements at 6 month follow-up.

	Everolimus (n=74)*	Bare (n=32)*	P-value**
Vessel volume (mm^3)	291 ± 82	296 ± 73	0.64
Stent volume (mm^3)	134 ± 28	139 ± 33	0.69
In-stent neo-intimal volume (mm^3)	10 ± 13	38 ± 19	<0.001
Luminal volume (mm^3)	124 ± 32	100 ± 31	0.04
In-stent volume obstruction (%)**	8.0 ± 10.4	28.1 ± 14.0	<0.001

* This final table contains an additional 13 patients not included in the 180-day report prepared for the sponsor. In 8 patients (4 in each group), an imputed stent length of 18mm was used due to non-continuous pullback. In a further 5 patients (all bare stent group) results were unavailable at the time of the 180-day report. (see Appendix)

** In-stent volume obstruction = 100*
(In-stent neo-intimal volume / Stent volume)

less neointimal hyperplasia was observed in the everolimus-stent group compared to the bare-stent group (10 ± 13 vs. 38 ± 19 mm^3, p<0.001) and similarly, significantly less volume obstruction, (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). Figure 4 is a cumulative curve of percentage volume obstruction. No in-stent volume obstruction was detected in almost half of the patients in the everolimus-stent group, whereas in the bare stent group, some degree of obstruction by neointima was present in all patients (Figure 4). No evidence of an "edge effect," aneurysm formation, in-stent thrombosis, persistent dissection or late incomplete apposition were observed

FIGURE 4

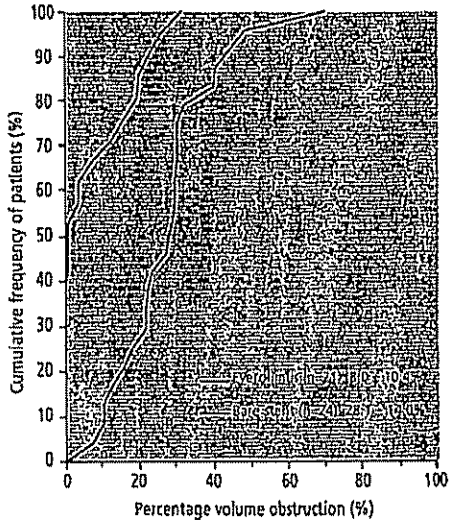

Fig. 4: Percentage in-stent volume obstruction versus cumulative frequency of patients. Values are expressed as mean ± standard deviation for each group.

Major adverse cardiac events

Major adverse cardiac events are listed in Table 4. There was one Q-wave myocardial infarction in the everolimus group in a patient who underwent additional revascularization for angina in a non-target vessel 18 days after the study procedure and suffered thrombosis of this non-study stent 12 days later. The everolimus stent was patent with no evidence of thrombus at the time of the thrombotic occlusion of the non study stent. One patient in the everolimus arm underwent a clinically driven target lesion revascularization at 3 weeks for symptomatic persistent dissection at the proximal edge left untreated at the time of the procedure. There were no clinically driven target revascularizations in the everolimus group for restenosis. There were six clinically driven target lesion revascularizations in the bare stent group, five were treated percutaneously for restenosis and the sixth by bypass surgery. No adverse effects were attributable to everolimus or the polymer coating of the stents.

Table 4. Hierarchical major adverse cardiac events at 180 days in per-treatment population*.

Event	Everolimus-stent n=76		Bare-stent n=28	
	n	%	n	%
Cardiac death	0	0	0	0
Myocardial infarction				
Q-wave	1‡	3.8	0	0
Non-Q-wave	0	0	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	1 §	3.8	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	2	7.7	6	21.4
Major adverse cardiac events	2	7.7	6	21.4

* One patient in each group withdrew consent after treatment
** No statistical significance was detected between groups for all endpoints tested.
‡ Q-wave MI due to thrombosis of a non-study stent in a non-target vessel.
§ Clinically driven TLR for persistent dissection proximal to the stent 3 weeks after the index procedure.

Discussion

The main finding of this randomized first-in-man study is that an everolimus-eluting stent coated with a durable polymer was associated with an in-stent angiographic late loss of 0.10 mm, significantly less than the corresponding bare cobalt chromium metal stent of 0.87 mm, which satisfied the primary endpoint of this trial and confirmed the efficacy of this system. Correspondingly, in-segment late loss was also significantly less in the everolimus-stent group.

Currently, two different drug-eluting systems (sirolimus and paclitaxel) are available. Although no published scientific comparative data is to date available, it appears that, from historical randomized trials, a difference of approximately 0.2 mm in-stent late loss exists between sirolimus and paclitaxel. Even if the impact of restenosis and MACE is currently unknown, some slight difference in restenosis rates and MACE can be expected. New devices should at least equal the incumbents in performance. This performance may be judged on late

loss, restenosis rate and / or the need for reintervention. With an in-stent late loss ranging from zero to 0.2 mm, it has been difficult to find a compound with the same efficacy, without resorting to the -limus family (Figure 5). With the sirolimus molecule being rather large and complex, it is therefore not surprising that major pharmaceutical companies have thoroughly explored its numerous analogues in order to develop a suitable competitor to sirolimus. The drug used in this study, everolimus differs from sirolimus by a substitution of a hydrogen radical/side-branch with a methyl sidechain

FIGURE 5

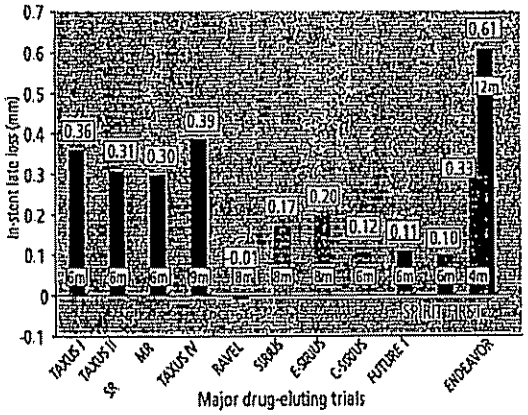

Fig. 5: Comparison of in-stent late loss from drug-eluting trials.

The reason for developing new compounds is to improve on the side effects of the existing compounds such as delayed healing with re-endothelialization and fibrin[11], early[12] and late stent thrombosis[13]. The success of the device lies in its three components - the drug, the polymer properties and the stent. The use of a sirolimus analogue is not in itself a guarantee of success since some of them have intrinsically, a potency in inhibition of up to 100 times less (e.g. tacrolimus), and some other analogues with equal *in vitro* inhibitory effects nevertheless fail to equally inhibit neointimal growth *in vivo*, because their duration of elution was suspected to be too short. However it has already been demonstrated that everolimus in clinical trials using a bioerodable polymer with a slower elution profile than sirolimus is effective in reducing late loss to below 0.2 mm[4]. Therefore the remaining challenge was to establish whether everolimus eluted from a durable polymer was also efficient and is addressed in this report

Although the 6-month results are promising, one year angiographic and IVUS follow-up results are awaited to confirm the long-term results of this device in light of recent findings regarding an increasing late loss seen with other devices over time.

At the time of the publication of RAVEL, it was argued that the restenosis rate of the bare stent was excessively high at 26%. Similarly, in the present trial the restenosis rate in the bare stent arm was 25.9%. Nevertheless, it must be emphasized that in both cases these restenosis rates correspond to the value predicted and derived from multivariate analyses including as determinant parameters vessel size, MLD post, incidence of LAD disease and diabetics. Of interest, the late loss of the bare stent groups in RAVEL and this study were similar, corresponding to their restenosis rates. This is at variance with the VISION registry, and publications on stent strut thickness, but may be explained by the mismatch in stent size and reference diameter.

This study was powered for late loss and not for clinical events, and it was not surprising that the 3 fold reduction in events failed to be statistically significant. At the time of trial design, safety studies with overlapping eluting-stents in animal models had not been completed, requiring the use of bare stents for bailout. As a result of this confounder, these patients were *a priori* excluded from the per-treatment analysis. This study was however designed as a first in man trial with everolimus on an untested new durable polymer in combination with a cobalt chromium stent

Acknowledgements

The authors would like to acknowledge the invaluable assistance of Susan Veldhof, RN, Cecile Dorange, MSc, Sophie Henry, MSEE from Guidant Europe, Diegem, Belgium for the conduct and reporting of this study.

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Appendix

Sponsor: Guidant Corporation, Santa Clara, California, USA.

Principal Investigator: Patrick W. Serruys (The Netherlands)

Executive Committee: P.W. Serruys (Principal Investigator and Chairman, Rotterdam, The Netherlands); Gary Johnson (Vice President of Regulatory Affairs/Clinical Research, Guidant Corporation); Stan Fink (Director of Clinical Research USA, Guidant Corporation).

Data Safety Monitoring Board (DSMB) - J.G.P. Tijssen, Amsterdam, The Netherlands; F.W.A. Verheugt, Nijmegen, The Netherlands; W. Wijns, Aalst, Belgium.

Clinical Events Committee (CEC) - J. Vos, Amphia Ziekenhuis, Breda, The Netherlands; B.J.W.M. Rensing, Sint Antonius Ziekenhuis, Nieuwegein, the Netherlands; C. Hanet, Clinique Universitaire de Saint-Luc, Brussels, Belgium.

Data management - Angiographic and IVUS core laboratories: Cardialysis BV, Rotterdam, The Netherlands; Data Coordination Centre and Site Monitoring: Guidant Europe, Diegem, Belgium.

The following investigators and institutions participated in the SPIRIT First trial:

Clinical sites: J.J. Piek, Academisch Medisch Centrum, Amsterdam, The Netherlands (18 patients); F.J. Neumann, Herzzentrum, Bad Krozingen, Germany (14 patients); P.W. Serruys, Thoraxcentre, Erasmus Medical Centre, Rotterdam, The Netherlands (5 patients); M. Wiemer, HZ Herzzentrum, Bad Oeynhausen, Germany (5 patients); A. Zeiher, Uni. Klinikum Frankfurt, Frankfurt, Germany (4 patients); E. Gruba, Heart Center Siegburg, Siegburg, Germany (4 patients); J. Haase, Red Cross Hospital, Frankfurt, Germany (4 patients); L. Thuesen, Skejby Sygehus, Aarhus, Denmark (4 patients); C. Hamm, Kerckhoff Klinik, Bad Nauheim, Germany (2 patients).

Table A2. Appendix: results of intra vascular ultra sound analysis as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Everolimus (N=29)	Bare (N=25)	p-value
Vessel volume (mm^3)	299 ± 87	284 ± 77	0.76
Stent volume (mm^3)	138 ± 30	139 ± 39	1.00
In-stent neo-intimal volume (mm^3)	11.2 ± 14.0	41.4 ± 20.1	<0.001
Luminal volume (mm^3)	126 ± 35	98 ± 34	0.06
In-stent volume obstruction (%)	8.6 ± 10.7	29.0 ± 13.9	<0.001

Table A1. Appendix: results of sub-segmental quantitative coronary angiographic analysis (Unmatched Pairs) as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Proximal edge			In-stent			Distal edge			In-segment analysis		
	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value
Mean luminal diameter (mm)												
After procedure	2.49 ± 0.44	2.57 ± 0.39	0.44*	2.34 ± 0.26	2.42 ± 0.31	0.41*	2.18 ± 0.44	2.25 ± 0.42	0.67*	2.07 ± 0.37	2.14 ± 0.37	0.74*
At 6 months	2.45 ± 0.46	2.19 ± 0.50	0.05*	2.28 ± 0.33	1.58 ± 0.42	<0.001*	2.18 ± 0.38	1.99 ± 0.46	0.19*	2.04 ± 0.40	1.53 ± 0.41	<0.001*
Late loss (mm)	0.10 ± 0.17	0.38 ± 0.38	0.01*	0.10 ± 0.23	0.84 ± 0.36	<0.001***	0.07 ± 0.20	0.26 ± 0.41	0.14*	0.09 ± 0.20	0.60 ± 0.36	<0.001*
Diameter stenosis (%)												
After procedure	10 ± 10	15 ± 9	0.13*	12 ± 4	15 ± 6	0.02*	17 ± 10	19 ± 9	0.39*	21 ± 8	24 ± 8	0.14*
At 6 months	12 ± 12	18 ± 17	0.21*	16 ± 8	39 ± 14	<0.001*	16 ± 10	20 ± 14	0.67*	22 ± 11	41 ± 14	<0.001*
Binary restenosis rates	4.3%	3.8%	1.00**	0.0%	26.9%	0.01**	0.0%	7.7%	0.49**	4.3%	34.6%	0.01**

* Two-sided Wilcoxon rank sum test ** Two-sided Fisher's Exact test *** One-sided t-test

EXHIBIT 8

EuroIntervention

One-year results of a durable polymer everolimus-eluting stent in *de novo* coronary narrowings (The SPIRIT FIRST Trial)

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This study was sponsored by Guidant Corporation, Santa Clara, California, USA.
Ms. Veldhof and Ms. Dorange are employees of Guidant Corporation. The other authors declare no conflict of interests.
Presented in part at The Scientific Sessions of The American Heart Association, Dallas, Texas, 13 - 16 November, 2005.

KEYWORDS
Coronary artery disease, eluting stent, everolimus, randomized trial

Abstract

Aim: Short-term results of durable polymer everolimus-eluting stents have shown significant improvements in clinical and angiographic outcomes. This report presents the 1-year clinical and angiographic data from the SPIRIT FIRST Trial.

Methods and results: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus and a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Of the 60 patients enrolled, a total of 56 patients (27 everolimus arm and 29 bare stent arm) were qualified to per-treatment analyses at 1 year. Quantitative angiographic and intravascular ultrasound (IVUS) analyses were performed. Angiographic late loss, IVUS neointimal volume obstruction and major adverse cardiac events (MACE) at 1 year were assessed as the study endpoints. At 1 year, the in-stent late loss and diameter stenosis of patients were 0.24 mm and 18% in the everolimus arm (n=20), as compared with 0.84 mm and 37% in the bare stent arm (n=25, $p < 0.001$). Significantly less neointimal hyperplasia was observed in the everolimus arm compared to the bare stent arm (neointimal volume, 13±9 mm^3 vs. 37±17 mm^3, $p < 0.001$; volume obstruction, 10±7% vs. 28±12%, $p < 0.001$). The overall MACE rate was 15.4% in the everolimus arm and 21.4% in the bare stent arm.

Conclusion: The safety and efficacy of everolimus-eluting stent with a durable polymer observed at 6 months was sustained at 1 year.

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Introduction

To date percutaneous coronary intervention (PCI) using drug-eluting stents is considered the most secure treatment option for *de novo* single coronary artery disease. The two clinically available stents coated with an anti-proliferative drug, sirolimus or paclitaxel, have shown promising clinical and angiographic outcomes as proven in several randomized trials[1-3]. Beside these two drugs, the efficacy of newly developed antiproliferative drugs has been clinically investigated[4-9] and their potent effects in preventing restenosis have been reported[5-9].

Everolimus is a powerful anti-proliferative agent and has shown effect in preventing rejection in kidney and heart transplantation[10-12]. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of DNA synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with the function of FRAP.

The SPIRIT FIRST clinical trial represents the first evaluation of the everolimus-eluting stent which studied the potential benefits of the local application of everolimus in a durable polymer in combination with a stent with a thin strut design[5]. Compared to identical bare metal stents, everolimus-eluting stents have demonstrated effective suppression of neointimal growth at 6 months[5]. This paper presents the 1-year clinical and angiographic/intravascular ultrasound (IVUS) follow-up results from the experience with the durable polymer everolimus-eluting stent.

Methods

Study population

The SPIRIT FIRST clinical trial was a prospective, controlled, randomized, single-blinded, parallel 2-arm, multicentre clinical evaluation of a durable polymer everolimus-eluting stent (XIENCE™ V, Guidant, Santa Clara, CA, USA) in patients with *de novo* native coronary artery lesions. Patient eligibility criteria, device description and study procedure were previously reported, along with 6-month clinical, angiographic and IVUS analyses[5]. Briefly, study patients had single *de novo* stenoses of < 18 mm lesion length, coverable by 1 study stent, > 50% diameter stenosis, and vessel reference diameter 3.0 mm as assessed by on-line quantitative coronary angiography (QCA). Patients were ineligible if they had any of the followings: evolving myocardial infarction; stenosis of an unprotected left main coronary artery, an ostial location, or located within 2 mm of a bifurcation; a lesion with moderate to heavy calcification, or an angiographically visible thrombus; a left ventricular ejection fraction < 30%; were awaiting a heart transplant, or had a contraindication to aspirin, clopidogrel, heparin and any other drugs related to this study.

Follow-up and study endpoint

Clinical evaluation was scheduled at 1, 6, and 12 months with annual evaluation up to 5 years. Angiographic and IVUS imaging was obtained at baseline, 6- and 12-month follow-up.

The primary endpoint was in-stent late loss at 6 months. The major secondary endpoint was percent (%) in-stent volume obstruction at 6 months based on IVUS analysis. Other secondary endpoints included the followings: a) in-stent late loss at 1 year; b) in-segment late loss at 6 months and 1 year including proximal and distal evaluations; c) in-stent% volume obstruction at 1 year; d) in-stent and in-segment% diameter stenosis at 6 months and 1 year; e) in-stent and in-segment angiographic binary restenosis (ABR) at 6 months and 1 year; f) persisting incomplete apposition, late incomplete apposition, aneurysm formation, thrombus, persisting dissection at 6 months and 1 year; g) major adverse cardiac events (MACE) rate in-hospital and at 1, 6, 9 months and annually up to 5 years. MACE is comprised of death, myocardial infarction (MI), or clinically driven target lesion revascularization (TLR); g) acute device, procedural and clinical success. All deaths that could not be clearly attributed to another cause were considered a cardiac death. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

Quantitative Coronary Angiography evaluation

QCA was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter, and% diameter stenosis. ABR was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD at post-procedure and MLD at follow-up.

Intravascular Ultrasound Analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased-array IVUS using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program (Curad B.V., Wijk bij Duurstede, The Netherlands) was used for automated 3-D reconstruction of the stented and the peri-stent segments. The lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. The stent volume (SV) and lumen volume (LV) were calculated according to Simpson's rule. The in-stent neointimal volume was calculated as "SV-LV". The % obstruction of the stent volume was calculated as in-stent neointimal volume/stent volume _100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[13].

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population. Acute success was analyzed on the safety population. The per-treatment evaluable population consisted of patients who had no bailout and no major protocol deviations. The data for each patient were reviewed in a blinded

manner to determine whether the patient should be included in this analysis population. Analyses based on the per-treatment evaluable population were as "treated". Patients were included in the treatment arm corresponding to the study stent actually received.

The overall sample size calculation for this trial was determined based on the primary endpoint of in-stent late loss at 6 months and on the following assumptions: a single comparison of active to control; one-tailed t-test, unequal and unknown variances in the 2 groups being compared; $\alpha = 0.05$; true mean difference between the control group and the treatment group is 0.48 mm. This assumption was made based on the results of VISION Registry (mean late loss = 0.83 mm)[14], SIRIUS trial (mean late loss = 0.17 mm)[2] and TAXUS IV trial (mean late loss = 0.39 mm)[15]. Assuming the true mean late loss for the treatment group was 0.35 mm, the difference between the control group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm. The standard deviation was assumed to be 0.56 mm in the control group and 0.38 mm in the treatment group (based on the results of VISION Registry study and SIRIUS trial with standard deviation for DES adjusted downward from 0.44 mm to 0.38 mm to take into account of 6-month angiography as opposed to 8-month angiography); approximately 20% rate of lost to follow-up or dropout; approximately 10% of patients with bailout stents; given the above assumptions, enrolling 30 patients per arm (analysis of 22 evaluable patients per arm) would have provided 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) provides more than 96% power. Binary variables were compared using Fisher's exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon's rank sum test. Time-to-event variables were compared with Kaplan-Meier analysis and the log rank statistic.

Results

A total of 60 study patients were randomized and consecutively enrolled at 9 investigational sites between December 2003 and April 2004. The safety population is composed of these 60 patients. Of the 60 patients, 3 were excluded from the per-treatment population (1 from the everolimus arm and 2 from the bare stent arm) because of bailout stenting (2) and major protocol deviation (1 patient on a heart transplant waiting list from bare stent arm). Hence the per-treatment population includes 56 patients (27 everolimus arm and 29 control) as illustrated in the trial profile (Figure 1). The control arm and the everolimus arm shared similar demographic characteristics except for patients with hypertension which was significantly higher in the everolimus group than in control (Table 1). Procedural characteristics were explained previously[5].

One-year quantitative coronary angiographic analysis (Table 2)

Nine patients did not have qualifying follow-up angiogram up to 1 year for the following reasons: a) patients withdrew from the clinical trial after the 30-day follow-up visit (1 patient in the everolimus

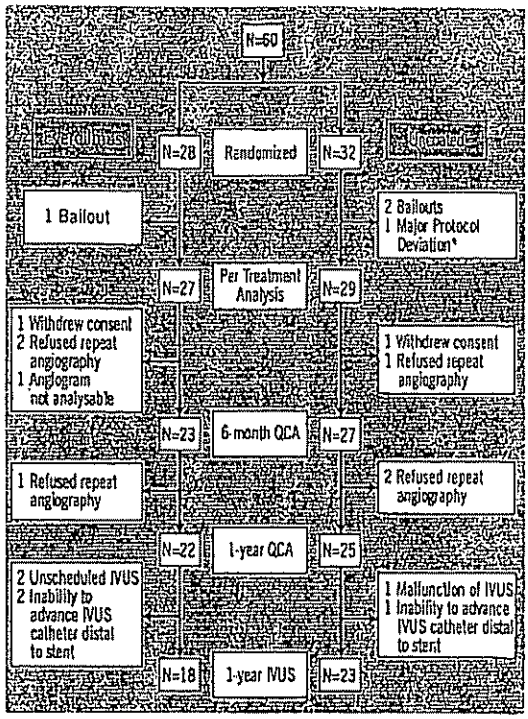

Figure 1. Flowchart of patients. QCA, quantitative coronary angiography; IVUS, intravascular ultrasound.

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus-eluting stent (n=27)	Bare metal stent (n=29)	All patients (n=56)
Age(yrs)	64±10	61±9	63±9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring Medication (%)	70	41	55
Hyperlipidemia requiring Medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left Anterior Descending	48	45	46
Left Circumflex	22	21	21
RCA	30	34	32
AHA / ACC# Lesion class (%)			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference vessel diameter (mm±SD)	2.61±0.40	2.71±0.28	2.66±0.34
Lesion length (mm±SD)	10.1±2.6	10.9±3.3	10.5±3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)
# AHA / ACC = American Heart Association / American College of Cardiology.

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Serial analysis)

	Proximal Edge			In Stent			Distal Edge			In Segment Analysis		
	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value
Reference vessel diameter (mm)												
After procedure	2.81±0.36	2.98±0.33	0.27	2.74±0.29	2.80±0.32	0.61	2.70±0.31	2.71±0.32	0.95	2.69±0.33	2.74±0.34	0.81
At 6 months	2.79±0.34	2.64±0.43	0.10	2.74±0.31	2.57±0.39	0.12	2.66±0.37	2.44±0.38	0.06	2.65±0.36	2.58±0.38	0.50
At 1 year	2.75±0.34	2.64±0.39	0.29	2.65±0.32	2.52±0.38	0.22	2.59±0.39	2.40±0.39	0.12	2.59±0.37	2.53±0.38	0.62
Minimal luminal diameter (mm)												
After procedure	2.56±0.44	2.60±0.43	0.93	2.40±0.25	2.42±0.26	0.91	2.29±0.38	2.20±0.45	0.54	2.15±0.32	2.11±0.37	0.56
At 6 months	2.47±0.49	2.15±0.51	0.04	2.28±0.33	1.53±0.40	< 0.001	2.23±0.32	1.99±0.46	0.08	2.07±0.38	1.49±0.39	< 0.001
At 1 year	2.44±0.47	2.12±0.48	0.03	2.16±0.37	1.58±0.44	< 0.001	2.26±0.38	1.96±0.43	0.05	2.01±0.41	1.52±0.42	< 0.001
Late loss (mm)												
At 6 months	0.09±0.19	0.45±0.42	<0.01	0.12±0.22	0.89±0.39	< 0.001	0.06±0.21	0.21±0.41	0.10	0.08±0.20	0.62±0.39	< 0.001
At 1 year	0.12±0.25	0.48±0.39	< 0.001	0.24±0.27	0.84±0.45	< 0.001	0.03±0.25	0.25±0.42	0.04	0.14±0.24	0.59±0.42	< 0.001
Diameter stenosis (%DS)												
After procedure	9±11	13±9	0.53	12±6	13±7	0.36	15±10	19±11	0.22	20±6	23±9	0.18
At 6 months	12±14	18±18	0.17	17±7	41±14	< 0.001	16±8	19±14	0.95	22±11	42±13	< 0.001
At 1 year	11±13	19±15	0.12	18±13	37±17	< 0.001	13±8	18±14	0.24	22±15	40±16	< 0.001

*Patients who underwent angiography at 6 months as well as 1 year.

arm and 1 in the control arm); b) patients refused (3 in the everolimus arm and 3 in the control arm); c) angiogram was not analyzable (1 in the everolimus arm). Serial angiographic follow-up data, which is reported in this paper, were available in 80.4% (45/56) of the per-treatment population, with 74.1% (20/27) in the everolimus arm and 86.2% (25/29) in the control arm (Table 2). The follow-up in-stent MLD was significantly larger in the everolimus arm than in the control arm and the preservation of MLD between 6 months and 1 year was observed (2.28±0.33 mm at 6 months; 2.16±0.37 mm at 1 year). The mean in-stent late loss and% diameter stenosis were 0.24 mm and 18%, respectively, in the everolimus-stent group, as compared with 0.84 mm and 37%, respectively, in the control arm ($p < 0.001$ for each comparison). Figure 2 shows the cumulative frequency of in-stent late loss immediately after the index procedure at 6 months and 1 year in each treatment group. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus-stent group than in the control arm ($p < 0.001$ for proximal and $p = 0.04$ for distal). The in-segment late loss was significantly less in the everolimus arm than in the bare stent arm ($p < 0.001$).

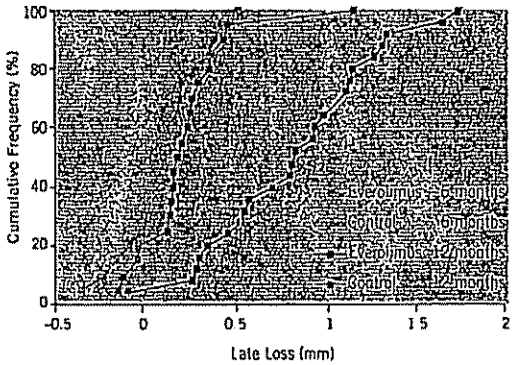

Figure 2. Cumulative frequency of late loss (in-stent) immediately after stenting.

One-year intravascular ultrasound evaluation (Table 3)

In this 1-year report, data in patients who underwent IVUS at 6 months as well as 1 year were presented to identify the volumetric change in serial IVUS examination. Forty-one patients (18 in the everolimus arm; 23 in the control arm) out of 47 patients with 1-year angiography underwent a 1-year IVUS examination. In the remaining

Table 3. Serial IVUS measurements at 1 year follow-up

		Everolimus-Stent (n = 18*)	Uncoated Stent (n = 23*)	P-value
Vessel volume (mm³)	6 months	296±90	291±74	0.89
	1 year	286±80	290±72	0.82
Stent volume (mm³)	6 months	137±31	138±31	0.94
	1 year	133±27	137±32	0.79
In-stent neo-intima volume (mm³)	6 months	9±12	39±20	< 0.001
	1 year	13±9	37±17	< 0.001
Luminal volume (mm³)	6 months	128±34	98±29	0.03
	1 year	120±30	100±28	0.15
In-stent volume obstruction (%)#	6 months	7±9	29±14	< 0.001
	1 year	10±7	28±12	< 0.001

* Patients who underwent IVUS at 6 months as well as 1 year.
# In-stent volume obstruction = 100*(In-stent neo-intima volume/Stent volume)

6 patients, IVUS was not available: 2 were not properly scheduled for IVUS, 2 inability to advance IVUS catheter distal to stent in the everolimus arm; 1 malfunction of IVUS, 1 inability to advance the IVUS catheter distal to the stent in the control arm. Of the 41 patients, 37 patients (16 in the everolimus arm; 21 in the control arm) had serial IVUS data. Everolimus-eluting stent was associated with a significantly reduced degree of in-stent neointimal hyperplasia as well as in-stent% volume obstruction compared to the bare metal stent (13±9 mm^3 vs. 37±17 mm^3, $p < 0.001$; 10±7% vs. 28±12%, $p < 0.001$), reaching a 64% reduction of the in-stent volume obstruction (Table 3). There was no late acquired or persisting stent malapposion observed either at 6 months or at 1 year.

Major adverse events and clinical outcomes

Table 4 provides results of MACE and target vessel failure for the time points of 1 year. Since the six months follow-up the 1-year results for the everolimus arm included 1 non-Q wave MI due to a spasm during the follow-up IVUS procedure and 2 additional TLRs by PCI. One of these patients had a delayed bailout (TLR) using a non-study drug eluting stent 21 days after the baseline procedure due to a dissection. In the control arm, 1 additional TLR by PCI was observed, this being the patient's 3rd TLR since the index procedure. The hierarchical MACE rate at 1 year was 15.4% for the everolimus arm and 21.4% for the bare stent arm ($p=0.59$). The MACE rate for the everolimus group increased from 7.7% (2/26) at 6 months to 15.4% (4/26) at 1 year. Three of the 4 overall MACE events in the everolimus group were non-study-device related events. One Q-wave MI was in a non-target vessel, one TLR was due to dissection during the procedure, and one non-Q-wave MI occurred during follow-up IVUS procedure. Total non-hierarchical clinically-driven TLR rates at 1 year were 7.7% in the everolimus arm and 21.4% in the control arm. No adverse effects related to everolimus or the durable polymer were noted. Kaplan-Meier survival estimates were performed for overall MACE (Figure 3). There was no stent thrombosis observed in both arms out to the 1-year time period.

Table 4. Hierarchical Major Adverse Cardiac Events at 1 year in Per-Treatment Population

Event	Everolimus Stent		Uncoated Stent	
	n=26	%	n=28	%
Cardiac death	0	0	0	0
Myocardial infarction	2	7.6	0	0
Q-wave	1	3.8	0	0
Non-Q-wave	1	3.8	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	2	7.7	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	4	15.4	6	21.4
Major adverse cardiac events	4	15.4	6	21.4

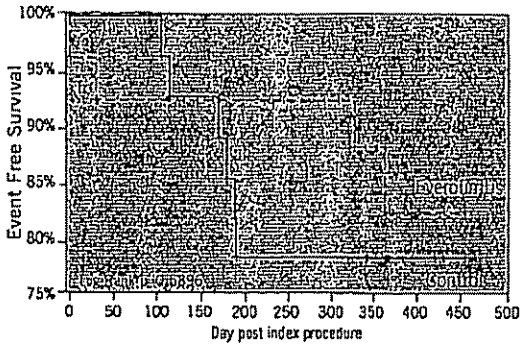

Figure 3. Kaplan-Meier survival curve: MACE. Since the 6-month time point, 1 non-Q wave MI due to a dissection during the follow-up IVUS procedure and 1 clinically-driven additional target lesion revascularization by PCI were observed in everolimus arm. In the control arm, 1 clinically-driven additional target lesion revascularization by PCI was performed.

Discussion

One-year clinical and angiographic follow-up from this trial demonstrates that the polymer-controlled release of everolimus from a coronary stent is safe and effective, with no late adverse effects. The superiority in efficacy, as measured by in-stent late loss, of everolimus-eluting stent as compared to bare stent was sustained at 1 year (71% reduction in late loss). The everolimus arm also maintained its superiority to the bare metal arm in the major secondary IVUS endpoint,% volume obstruction, at 1 year (64% reduction). In addition, the everolimus arm also continued to show significantly lower neointimal volume than the bare stent arm at 1 year (65% reduction).

The current strategy of local drug delivery using sirolimus and paclitaxel is the most promising approach to prevent restenosis, but, at the same time, the strategy has the potential liability for impairing endothelial recovery. Developing new compounds may improve on the potential side effects of the current drug-eluting stents, such as delayed healing with re-endothelialization[16] and fibrin[17], early[18] and late stent thrombosis[19]. In this trial, neither stent thrombosis nor other adverse effects related to the drug/durable polymer was observed out to the 1-year time point. On the other hand, an *in vitro* study has shown that sirolimus enhances tissue factor in human endothelial cell[20]. Effect of everolimus on endothelial cell and its similarity or difference compared to sirolimus will have to be investigated. The significant differences between sirolimus- and paclitaxel-eluting stents have recently been reported to likely exist with regard to angiographic as well as clinical outcomes[21,22]. "New comers" following these 2 pioneers could be competitors if they can, at least, demonstrate performance as effective as these 2 drug-eluting stents. Studies have suggested that angiographic assessment of late loss is associated with an increased restenosis rate[23,24] as well as a higher risk of TLR[25]. However, it still remains to be determined how to interpret the significance of the slight increase in late loss from 6 months (0.12 mm) to 1 year (0.24 mm) observed in this study stent. Moreover, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial IVUS analyses in some trials

as documented in everolimus-eluting stent (in-stent volume obstruction, 7% at 6 months to 10% at 1 year), which may raise a concern about potential late catch-up phenomenon of DES[26]. Recent head-to-head comparative studies between sirolimus- and paclitaxel-eluting stent are still limited to short-term results[21,22,25,27-30]. Beneficial short-term outcomes do not necessarily translate in long-term efficacy. For example, late catch-up phenomenon has been experienced in vascular brachytherapy[31]. In this respect, the follow-up period of 1 year still seems relatively short to assess the durable safety and efficacy of one drug-eluting stent. However, neither sirolimus- nor paclitaxel-eluting stent have been associated with gradually increasing MACE over the years[32,33]. Therefore, we could expect a similar lasting treatment effect of this new eluting stent.

Study limitation

This study with a small patient population provided only safety and efficacy data. Two larger single-blind, randomized controlled studies (The SPIRIT II and SPIRIT III) further evaluating this study stent compared to the paclitaxel-eluting stent for the treatment of coronary artery disease are under way.

Conclusions

At 1 year, this trial demonstrated that the treatment effect observed at 6 months was sustained at 1 year for everolimus-eluting stent. The in-stent and in-segment late loss in the everolimus arm was reduced by 71% and 78% compared to those in the bare metal arm, respectively. These observations were consistent with IVUS measurements. The 1-year results showed a reduction of neointimal volume by 65% as compared to bare metal stent. A small increase in % volume obstruction in event-free patients was observed from 6 to 12 months, but is considered clinically insignificant. Both the angiographic and IVUS measurements showed that the patency of the target vessel treated with everolimus-eluting stent was maintained at 1 year.

Acknowledgement

The authors are grateful to the invaluable assistance of Stan Fink and Danny Detlège (Guidant, Santa Clara and Guidant Europe) for their valued assistance in reporting this study.

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EXHIBIT I

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

JUDGE LYNCH

JOHNSON & JOHNSON, a New Jersey Corporation,

Plaintiffs,

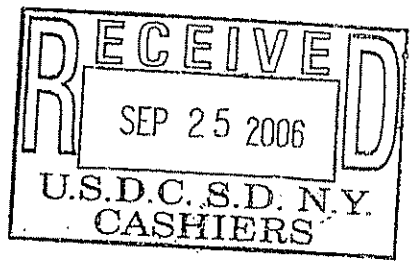
- against -

GUIDANT CORPORATION, an Indiana Corporation, BOSTON SCIENTIFIC CORPORATION, a Delaware Corporation, and ABBOTT LABORATORIES, an Illinois Corporation,

Defendants.

Civil Action No. 06 CV 7685

Complaint



Johnson & Johnson ("J&J"), by its attorneys, Kramer Levin Naftalis & Frankel LLP, for its complaint against Guidant Corporation ("Guidant"), Boston Scientific Corporation ("Boston Scientific") and Abbott Laboratories ("Abbott"), alleges as follows:

I. Nature of the Action

1. This action arises out of the highly publicized takeover battle between J&J and Boston Scientific to acquire Guidant. While Boston Scientific ultimately succeeded in its takeover bid for Guidant, it did so only because Guidant leaked confidential information to a third party, Abbott, for the purpose of arranging a prepackaged divestiture of significant Guidant businesses to Abbott. Based on these disclosures, which were in material breach of the terms of Guidant's merger agreement with J&J, Abbott agreed to enter into a divestiture and financing agreement with Boston Scientific, which allowed Boston Scientific to make an offer for Guidant that would not require a lengthy and uncertain antitrust review. This, in turn, allowed Guidant to accept Boston Scientific's offer as "superior" to J&J's offer and to terminate the agreement with

J&J. Thus, Guidant's breach of its agreement with J&J, and Boston Scientific's and Abbott's tortious interference with that agreement, deprived J&J of the benefit of the bargain of its merger with Guidant and caused it to suffer damages.

2. In December 2004, J&J and Guidant entered into a merger agreement that provided that J&J would pay $25.4 billion to acquire Guidant, or $76 per Guidant share (the "Initial Merger Agreement"). Guidant's shareholders approved the merger. The price was subsequently changed to $21.5 billion, or $63.08 per share, as a result of various product recalls and legal problems that surfaced at Guidant. In this regard, the parties entered into an Amended and Restated Agreement and Plan of Merger dated November 14, 2005 (the "Merger Agreement").

3. Like any large multi-national acquisition, the merger was subject to antitrust approval by U.S., European Union and other foreign regulators. Over the following ten months, J&J reached an agreement with domestic and foreign regulators which, among other things, would grant a non-exclusive license for certain patents to Abbott to facilitate antitrust approval for the merger with Guidant.

4. Pending the closing of the merger, Guidant was prohibited under the express terms of the Merger Agreement from soliciting alternative offers and had limited ability to respond to an unsolicited bid from another party. Under the "No Solicitation" provision in the Merger Agreement — which was designed to prevent Guidant from using the Merger Agreement to solicit higher offers — Guidant was prohibited from providing confidential business information to any company, or its representatives, unless that company was making an unsolicited "Takeover Proposal" (*i.e.*, a proposal to acquire 15% or more of Guidant) under

terms that were likely to result in a bid that constituted a "Superior Proposal" to the merger with J&J. Guidant also could not facilitate or cooperate with a Takeover Proposal other than through discussions with, and disclosures to, the person making such a Takeover Proposal. Under no circumstances could Guidant provide confidential business information to or discuss or negotiate with any third party that was not making a bona fide Takeover Proposal.

5. In December 2005, just as the J&J/Guidant merger was about to close, Boston Scientific made a bid to acquire Guidant for $25 billion, or $72 per Guidant share. While nominally higher in price than the renegotiated deal with J&J, Boston Scientific's offer was fraught with uncertainty and timing issues that rendered its proposal patently inferior to the merger with J&J. For example, unlike J&J, which had spent much of the past year resolving potential antitrust issues by entering into a License Agreement with Abbott and a Consent Decree with the regulators, Boston Scientific had not even begun the pre-merger notification process, much less resolved its own antitrust issues, at the time of its announced bid.

6. After receiving a Takeover Proposal from Boston Scientific, Guidant's management allowed Boston Scientific to perform limited due diligence. What Guidant did not disclose until after the fact, however, was that it simultaneously allowed Abbott — a third party with absolutely no right to receive any confidential information from Guidant under the No Solicitation provision and which had already agreed to facilitate J&J's bid — an even "deeper dive" into Guidant's confidential business information to determine whether Abbott would now be willing to enter into a pre-packaged divestiture agreement with Boston Scientific to clear any antitrust hurdles. In so doing, Guidant materially breached the No Solicitation provision of its Merger Agreement with J&J.

7. Based on the information disclosed to it by Guidant, Abbott and Boston Scientific entered into an agreement to divest Guidant's entire vascular intervention ("VI") business and other assets and Boston Scientific then made a formal proposal to acquire Guidant for $72 per share. On January 25, 2006, after several counter-proposals from J&J and Boston Scientific, Guidant announced that it was terminating the Merger Agreement with J&J and entering into an acquisition agreement with Boston Scientific for $27 billion.

8. Abbott would not have agreed to a pre-packaged divestiture without the confidential information it received in violation of the "No–Solicitation" provision of J&J's Merger Agreement with Guidant. Without a pre-packaged divestiture agreement, Boston Scientific could not have made a proposal that would have been acceptable to Guidant's Board of Directors or shareholders, both because it would have been conditioned on reaching an agreement with Abbott or some other party to resolve antitrust issues and would have entailed a lengthy antitrust review, the outcome of which would have been uncertain.

9. Guidant could have terminated its Merger Agreement with J&J and then provided information to Abbott, but would then have lost the ability to keep J&J bound to a deal if a transaction with Boston Scientific failed to materialize. Guidant was also able to use its agreement with J&J to better its negotiating position with Boston Scientific. By keeping J&J contractually bound while it facilitated what was ultimately declared a Superior Proposal from Boston Scientific, Guidant acted in bad faith and in violation of its contractual restrictions pending the closing of the Merger Agreement with J&J.

10. Boston Scientific and Abbott were well aware that Guidant had entered into the Merger Agreement with J&J; indeed, Abbott had agreed to facilitate consummation of

that transaction before it began dealing with Boston Scientific behind J&J's back. By their actions, these defendants induced Guidant to breach that agreement by disclosing confidential information to Abbott with the goal of ensuring the success of Boston Scientific's Takeover Proposal.

11. As a result of Guidant's willful and material breach, and the tortious interference by Boston Scientific and Abbott, J&J was deprived of the benefit of its merger agreement and suffered damages that it now seeks to recover through this action.

II. Jurisdiction and Venue

12. The Court has diversity jurisdiction over the subject matter of this case, under 28 U.S.C. § 1332, because this case arises among citizens of different states and the amount in controversy exceeds the sum or value of $75,000.

13. The Court has jurisdiction over the parties, each of which is a corporation doing business in the State of New York, and jurisdiction to grant all the relief requested by J&J.

14. Venue is proper in the Southern District of New York because one party, Guidant, is subject to and has consented to the jurisdiction of this Court and there is no other district in which this action may otherwise be brought.

III. The Parties

15. J&J is a New Jersey corporation with its headquarters and principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey. Through its operating subsidiaries, J&J is a multi-national manufacturer and distributor of health care, surgical, biotechnology, and personal hygiene products, as well as a provider of related services

for the consumer, pharmaceutical, medical devices, and diagnostics markets. J&J has more than 230 operating companies, which employ approximately 116,000 people in 57 countries and sell products in the United States and around the world.

16. Guidant is an Indiana corporation having a principal place of business at 11 Monument Circle, Indianapolis, Indiana. It is now a wholly-owned subsidiary of Boston Scientific. Guidant designs, develops, and markets cardiovascular medical products, including pacemakers and implantable defibrillators.

17. Boston Scientific is a Delaware corporation having a principal place of business at One Boston Scientific Place, Natick, Massachusetts. Boston Scientific develops, manufactures and markets a range of medical devices and procedures.

18. Abbott is an Illinois corporation having a principal place of business at 100 Abbott Park Road, Abbott Park, Illinois. Abbott develops, manufactures, and markets pharmaceutical and nutritional products, as well as surgical and diagnostic devices.

IV. Background Facts

(a) J&J and Guidant Engage in Confidential Merger Discussions

19. Among other products, J&J, through its subsidiary Cordis Corporation ("Cordis"), markets medical devices for the treatment of cardiovascular disorders, including a coronary stent known as the Cypher stent. A stent is a metallic device surgically inserted to keep arteries open after balloon angioplasty to clear blockages. The Cypher stent provides a mechanical scaffold to keep the vessel open while a drug is slowly released from the stent to

prevent the build-up of new tissue that re-clogs the artery. Stents that work with drugs like this are known in the industry as drug-eluting stents ("DES").

20. DES account for over 80% of the U.S. coronary stent market. Aside from Cordis, Boston Scientific is the only other company that markets DES in the U.S., with Cordis having approximately a 45% market share and Boston Scientific approximately a 55% market share. Guidant, Abbott and another company called Medtronic are all in the process of seeking, or undertaking the preparations necessary to seek, approval of the Food and Drug Administration to market DES in this country.

21. During the fall 2004, J&J engaged in discussions with Guidant about the possibility of entering into a business transaction whereby J&J would acquire Guidant. The acquisition of Guidant represented an opportunity for J&J to expand its business into the cardiac rhythm management market for implantable pacemakers and defibrillators.

22. On or about August 4, 2004, J&J and Guidant entered into a Confidentiality Agreement that provided that information exchanged between J&J and Guidant would be used solely for the purpose of exploring a possible negotiated business arrangement and not for any other business or competitive purpose.

(b) J&J and Guidant Enter into a Merger Agreement

23. On December 15, 2004, J&J and Guidant entered into the Initial Merger Agreement pursuant to which J&J agreed to pay $25.4 billion in cash and stock or $76 per share to acquire Guidant. The closing of the merger was conditioned on (i) approval of the deal by Guidant shareholders, (ii) approval for listing on the New York Stock Exchange of newly registered J&J stock for issuance to Guidant shareholders, (iii) regulatory approval of the

transaction, including any divestitures, from U.S. and European Commission antitrust authorities, and (iv) the accuracy of the representations and warranties set forth in the agreement.

24. With Guidant's assistance, J&J prepared and filed with the Securities and Exchange Commission a Registration Statement on Form S-4 in connection with the issuance of J&J stock in the merger, as well as a Proxy Statement for the Merger that was included as a Prospectus.

25. Guidant gave notice of, convened, and held a meeting of its shareholders solely for the purpose of obtaining shareholder approval of the merger. On or about April 27, 2005, Guidant shareholders approved the merger.

26. J&J also sought the necessary antitrust clearance for the merger in the United States, Europe, and Canada. To this end, J&J filed a pre-merger notification under the Hart-Scott-Rodino Antitrust Act of 1976 with the Federal Trade Commission ("FTC") on January 18, 2005.

27. In discussions with the FTC, the agency objected to the proposed transaction on the ground that a merger between one of two actual competitors in the DES market with one of the three potential competitors would lessen competition in that market. On August 12, 2005, J&J and Abbott entered into a License Agreement whereby J&J granted Abbott a non-exclusive license to certain patents in the DES field in the event the transaction was consummated in order to increase the likelihood that Abbott would successfully enter the DES market. After lengthy negotiations, and based in part on the agreement between J&J and Abbott, the FTC and J&J entered into a Consent Order on November 2, 2005 to resolve the FTC's antitrust concerns.

28. In the meantime, numerous regulatory and legal problems surfaced involving Guidant products being recalled, lawsuits against Guidant being filed, and Guidant being investigated by the New York Attorney General. On October 18, 2005, J&J announced that the company was considering alternatives to its proposed acquisition of Guidant and on November 7, Guidant sued J&J claiming a breach of the Initial Merger Agreement. On November 14, Guidant accepted a revised offer of $21.5 billion, or $63.08 per Guidant share, the Merger Agreement was executed and the lawsuit was discontinued.

(c) The Merger Agreement Contained Strict Limitations on Guidant's Ability to Solicit or Cooperate with Competing Bids, Designed to Protect the Benefit of J&J's Bargain

29. Pursuant to the Merger Agreement, Guidant was prohibited from either (i) soliciting, initiating or knowingly encouraging, or taking any other action designed to, or which could reasonably be expected to, facilitate, any competing proposal to acquire Guidant or (ii) entering into, continuing or otherwise participating in any discussions or negotiations regarding, or furnishing to any person any information, or otherwise cooperating with any such proposal. These restrictions were designed to prevent Guidant from using the J&J offer as a means of obtaining higher bids for the company.

30. In particular, Section 4.02 of the Merger Agreement, titled "No Solicitation," provided as follows:

> The Company [*i.e.*, Guidant] shall not, nor shall it authorize or permit any of its Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, "Representatives") retained by it or any of its Subsidiaries to, directly or indirectly through another person, *(i) solicit, initiate or knowingly encourage, or take any other action designed to, or which could reasonably be expected to, facilitate, any Takeover Proposal or (ii) enter into, continue or otherwise*

> *participate in any discussions or negotiations regarding, or furnish to any person any information, or otherwise cooperate in any way with, any Takeover Proposal.* (Emphasis added).

31. Section 4.02 of the Merger Agreement defined a "Takeover Proposal" as basically a bid for at least 15% of Guidant's assets or businesses:

> The term "Takeover Proposal" means any inquiry, proposal or offer from any person relating to, or that could reasonably be expected to lead to, any direct or indirect acquisition or purchase, in one transaction or a series of transactions, of assets (including equity securities of any Subsidiary of the Company) or businesses that constitute 15% or more of the revenues, net income or assets of the Company and its Subsidiaries, taken as a whole, or 15% or more of any class of equity securities of the Company, any tender offer or exchange offer that if consummated would result in any person beneficially owning 15% or more of any class of equity securities of the Company, or any merger, consolidation, business combination, recapitalization, liquidation, dissolution, joint venture, binding share exchange or similar transaction involving the Company or any of its Subsidiaries pursuant to which any person or the shareholders of any person would own 15% or more of any class of equity securities of the Company or of any resulting parent company of the Company, in each case other than the transactions contemplated by this Agreement.

32. Notwithstanding these provisions, and in order to allow Guidant's directors to meet their fiduciary obligations to Guidant's shareholders, the Merger Agreement provided that if Guidant's Board of Directors, in consultation with outside legal counsel and a qualified financial advisor, determined that an unsolicited Takeover Proposal constituted or was reasonably likely to lead to a "Superior Proposal," as defined below, then, and only then, Guidant could (i) provide information to the "person making such Takeover Proposal (and its Representatives)," pursuant to an appropriate confidentiality agreement and as long as Guidant simultaneously provided (or already had provided) the information to J&J, and/or (ii) "participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives)."

33. In this regard, Section 4.02 provided as follows:

> Notwithstanding the foregoing, at any time prior to obtaining the Shareholder Approval, in response to a bona fide written Takeover Proposal that the Board of Directors of the Company reasonably determines (after consultation with outside counsel and a financial advisor of nationally recognized reputation) constitutes or is reasonably likely to lead to a Superior Proposal, and which Takeover Proposal was not solicited after the date hereof and was made after the date hereof and did not otherwise result from a breach of this Section 4.02(a), the Company may, subject to compliance with Section 4.02(c), (x) furnish information with respect to the Company and its Subsidiaries to the person making such Takeover Proposal (and its Representatives) pursuant to a customary confidentiality agreement not less restrictive to such person than the confidentiality provisions of the Confidentiality Agreement, *provided* that all such information has previously been provided to Parent or is provided to Parent prior to or substantially concurrent with the time it is provided to such person, and (y) participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives) regarding such Takeover Proposal.

34. As further defined in Section 4.02, "Representatives" of a person making a Takeover Proposal included only that person's "Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, 'Representatives')." Guidant was expressly prohibited from giving information to, or participating in discussions with, any other persons.

35. Whether a Takeover Proposal constituted or likely would lead to a Superior Proposal was to be based not only on its financial terms, but also on whether it was "reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal." Thus, under Section 4.02:

> The term "Superior Proposal" means any bona fide offer made by a third party that if consummated would result in such person (or its shareholders) owning, directly or indirectly, more than 80% of

> the shares of Company Common Stock then outstanding (or of the shares of the surviving entity in a merger or the direct or indirect parent of the surviving entity in a merger) or all or substantially all the assets of the Company, which the Board of Directors of the Company reasonably determines (after consultation with a financial advisor of nationally recognized reputation) to be (i) more favorable to the shareholders of the Company from a financial point of view than the Merger (taking into account all the terms and conditions of such proposal and this Agreement (including any changes to the financial terms of this Agreement proposed by Parent in response to such offer or otherwise)) and (ii) *reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal.* [Emphasis added]

36. In sum, under the Merger Agreement, Guidant could not solicit any Takeover Proposal from another person. In the event that it received an unsolicited Takeover Proposal, which it determined upon consultation with its legal and financial advisors was or could become a Superior Proposal, Guidant could furnish information to, and conduct discussions with, only the person (or its Representatives) making such a Takeover Proposal.

37. The Merger Agreement also provided that in the event Guidant's Board received a Superior Offer, Guidant was required to notify J&J of the terms of that offer and give J&J five business days to make a competing offer, which Guidant would be required to consider before it could terminate the Merger Agreement without a breach.

(d) Boston Scientific Makes a Last-Minute Bid, and Guidant Breaches the Merger Agreement to Facilitate Turning It into a Superior Proposal

38. On December 5, 2005, before the merger between J&J and Guidant had closed, Boston Scientific announced a bid for Guidant, offering $25 billion, or $72 per share. While nominally higher in price than the J&J deal, Boston Scientific's offer was contingent upon, among other things, receiving regulatory approval and was therefore subject to uncertainty and delay.

39. On January 8, 2006, Boston Scientific submitted a formal proposal to acquire Guidant for $72 per share. As part of this formal offer, Boston Scientific also announced that it had entered into an agreement with Abbott to divest Guidant's VI and endovascular businesses to Abbott, as well as to share rights to Guidant's DES program, in order to facilitate prompt antitrust review and approval. Abbott also agreed to provide a $700 million loan to Boston Scientific.

40. Based on statements made in a January 9, 2006 conference call with analysts to discuss the Boston Scientific proposal, it became clear that Guidant had cooperated with and facilitated Boston Scientific's Takeover Proposal by impermissibly providing confidential information to Abbott. This in turn enabled Boston Scientific to enter into the agreement with Abbott, which was critical to Boston Scientific's ability to have its offer declared by Guidant as a Superior Proposal and thereby have it accepted in lieu of the J&J transaction.

41. On the conference call, Larry Best, Chief Financial Officer for Boston Scientific, emphasized the importance of the agreement with Abbott to Boston Scientific's Takeover Proposal. In Mr. Best's words, the Abbott agreement was "critically important not only for the quick completion of the Guidant acquisition but also for the business prospects of the combined company." Mr. Best explained: "As we said when we announced our initial proposal our intention was to divest Guidant's vascular intervention and endovascular business in an effort to obtain rapid antitrust approval for the Guidant acquisition. Therefore, we have executed a binding agreement with Abbott. Abbott will buy Guidant's VI and endovascular businesses when we complete this transaction with Guidant."

42. During the Q&A session at the end of the call, one analyst asked Boston Scientific's Chief Operating Officer, Paul LaViolette, whether Boston Scientific had "seen part of the [Guidant DES] data as a part of your due diligence and if not, is there some contingency that exists for Abbott should the [Guidant DES] data prove disappointing . . . ?"

43. Electing to respond to this question himself, Mr. Best was quoted as saying:

> Let me explain the due diligence process. As you can imagine, Guidant, you know was very protective of their program in terms of our doing due diligence. *We had the opportunity to do a certain level of due diligence. Abbott had the opportunity to do a much deeper dive on due diligence.* My understanding from their due diligence is that they were very impressed with the data and what they found, and that is how they came up with the valuation and the decision to move forward. (Emphasis added).

44. Thus, at some point in time between Boston Scientific's announcement of its bid for Guidant on December 5, 2005, and Boston Scientific's submission of a formal proposal on January 8, 2006, Guidant not only allowed Boston Scientific to conduct due diligence on it businesses but also disclosed even more confidential business information to Abbott — which had no independent right to receive any information and was prohibited from receiving any information under the Merger Agreement — about its VI and endovascular businesses.

45. As a result of the "deeper dive" it was permitted into Guidant's confidential business information, Abbott was able to make a "decision to move forward" and agree to acquire the entire VI business and other assets that Boston Scientific needed to divest to expedite antitrust regulatory approval of its proposed acquisition of Guidant. Without these

agreements, Boston Scientific's Takeover Proposal would not have been viable, much less superior to J&J's.

(e) Guidant's Impermissible Disclosures Constituted a Willful and Material Breach of the Merger Agreement

46. Immediately upon learning that Guidant had divulged confidential business information to Abbott, in breach of the No Solicitation provision of the Merger Agreement, J&J's General Counsel raised the issue with Guidant's General Counsel. In a follow-up letter dated January 23, 2006, J&J's General Counsel wrote to Guidant noting the apparent breach of Section 4.02 of their Merger Agreement and demanding an explanation. In response, Guidant's General Counsel attempted to justify Guidant's actions by, among other things, claiming that "Boston Scientific brought Abbott into the transaction as part of Boston Scientific's 'Takeover Proposal'" and that Abbott was a "joint bidder" for Guidant along with Boston Scientific. The matter remained unresolved.

47. Abbott was not a "joint-bidder" for Guidant. Abbott did not make a Takeover Proposal either on its own or in conjunction with Boston Scientific and, therefore, was not entitled to receive any confidential information from Guidant. Nor was Abbott a "Representative" of Boston Scientific, as that term is defined in Section 4.02 of the Merger Agreement. Rather, at all times Abbott was a third party divestiture candidate dealing at arms' length with Boston Scientific in negotiating the acquisition of certain businesses that would be divested in the event that Boston Scientific's Takeover Proposal was accepted.

48. As Boston Scientific itself noted during the January 9 conference call, an executed agreement with Abbott was critically important both to rapid antitrust approval of a potential acquisition by Boston Scientific and to the perceived business prospects of the

combined company. Just as J&J entered into a Licensing Agreement with Abbott in anticipation of closing its Merger Agreement with Guidant, Boston Scientific needed to enter into a much more extensive agreement with Abbott — divesting entire businesses — to ease antitrust approval of its own otherwise inferior proposal to acquire Guidant. By leaking confidential information to Abbott, a third-party divestiture candidate, Guidant, in violation of the No Solicitation restrictions in its Merger Agreement with J&J, thus knowingly and willfully facilitated Boston Scientific's Takeover Proposal becoming a Superior Proposal.

(f) Guidant Deems Boston Scientific's Offer to be a "Superior Proposal"

49. On January 10, 2006, Guidant's Board of Directors met to consider whether Boston Scientific's offer was a "Superior Proposal."

50. Faced with the prospect of losing the transaction that it had pursued for more than a year, J&J chose to reconsider the amount it was willing to offer for Guidant. On January 11, J&J and Guidant announced a revised Merger Agreement, raising the price to $68.06 per Guidant share. On the next day, however, Boston Scientific improved its own offer to $73 per Guidant share. The following day, January 13, 2006, J&J and Guidant announced a further revision to their Merger Agreement, raising the acquisition price to $71 per share, but once again, on January 17, 2006, Boston Scientific raised its offer, this time to $80 per share.

51. Later in the day on January 17, 2006, Guidant's Board announced that Boston's bid was deemed a "Superior Proposal" to the existing deal with J&J. On January 25, 2006, Guidant announced that it was terminating the Merger Agreement with J&J, as it was entitled to do upon determining that there was a Superior Proposal, and entering into an acquisition agreement with Boston Scientific for $27 billion. J&J ultimately received a $705

million "termination fee" under the terms of its Merger Agreement. However, as the Merger Agreement itself makes clear, "no such termination shall relieve any party hereto from any liability or damages resulting from the willful and material breach by a party of any of its representations, warranties, covenants or agreements set forth in this Agreement." (Merger Agreement at § 7.02).

52. As a result of Guidant's willful and material breach of the No Solicitation provision of the Merger Agreement, which facilitated Boston Scientific's Takeover Proposal through the prohibited confidential disclosures to third-party divestiture candidate Abbott, J&J was wrongfully deprived of the full benefits of its bargain and suffered damages that it now seeks to recover.

V. Claims for Relief

First Cause of Action for Breach of Contract (Against Defendant Guidant)

53. J&J repeats and realleges the allegations of paragraphs 1 to 52.

54. J&J entered into a valid, binding contract embodied in the Merger Agreement. A material term of the Merger Agreement was a "No Solicitation" clause, as set forth in Section 4.02 of the Merger Agreement. The No Solicitation clause was designed to protect the terms of the bargain that the parties struck, pending the closing of their transaction, while providing Guidant with the limited ability to receive and negotiate unsolicited alternative proposals.

55. Assuming that Boston Scientific's December 5, 2005 bid could be viewed as reasonably likely to lead to a Superior Proposal, Guidant was only permitted to provide confidential information to Boston Scientific and its Representatives, as defined in the Merger Agreement. Since Abbott was neither a person making a Takeover Proposal nor a Representative of Boston Scientific, but only a third-party divestiture candidate, permitting Abbott to take a "deeper dive" into Guidant's confidential information was a clear breach of the Merger Agreement.

56. This breach went to the heart of J&J's bargain, facilitating a competing bid by providing confidential information to a person not entitled to receive such information under the No Solicitation clause.

57. The breach was also material and harmed J&J. Had Abbott not been provided with Guidant's confidential business information, Abbott would not have been able to enter into the divestiture agreement, which in turn facilitated and enabled Boston Scientific's Takeover Proposal to be viewed as a Superior Proposal.

58. As a result of Guidant's willful and material breach, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

59. J&J made reasonable and diligent attempts to mitigate its damages.

Second Cause of Action
for Breach of the Implied Duty of Good Faith and Fair Dealing
(Against Defendant Guidant)

60. J&J repeats and realleges the allegations of paragraphs 1 to 52.

61. As a matter of common law, as well as the law of the State of Indiana, every contract imposes on the parties thereto an implied duty of good faith and fair dealing.

62. Defendant Guidant breached the implied duty of good faith and fair dealing by negotiating and facilitating a competing Takeover Proposal from another party, Boston Scientific, during the time that it was party to a binding Merger Agreement with J&J, in violation of the Merger Agreement.

63. Guidant could have terminated the Merger Agreement with J&J, paid the termination fee, and assumed the risk of being able to negotiate and enter into an alternative deal with Boston Scientific, subject to the uncertainty of being able to consummate a divestiture and the inevitable delay and uncertainty of antitrust regulatory review. Instead, Guidant surreptitiously facilitated an alternative proposal with Boston Scientific, through the prohibited disclosure of confidential information to Abbott, a third party divestiture candidate. Guidant thus used the Merger Agreement to negotiate a better offer in breach of its implied duty of good faith and fair dealing.

64. As a result of Guidant's breach of the implied duty of good faith and fair dealing, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

Third Cause of Action
For Tortious Interference with Contract
(Against Defendants Boston Scientific and Abbott)

65. J&J repeats and realleges herein the allegations of paragraphs 1 to 52.

66. Boston Scientific and Abbott were aware that J&J had entered into a binding Merger Agreement with Guidant and were aware that the Merger Agreement prohibited the disclosure of confidential information to third parties.

67. Boston Scientific and Abbott intentionally induced Guidant to breach the Merger Agreement with J&J by disclosing confidential business information to Abbott.

68. Boston Scientific and Abbott thus knowingly, intentionally, and maliciously interfered with J&J's binding contract to acquire Guidant under the terms of the Merger Agreement that was on the verge of closing.

69. Abbott emerged from its prohibited due diligence review with a clear picture of Guidant's businesses that enabled it to proceed expeditiously with a divestiture agreement, which in turn facilitated Boston Scientific's ability to make a "Superior Proposal" to Guidant.

70. As a result of Guidant's breaches and Boston Scientific's and Abbott's tortious interference with J&J's Merger Agreement and prospective business opportunity, J&J was damaged.

Prayer for Relief

Wherefore, Plaintiff J&J respectfully requests the following relief:

(i) that the Court find that Guidant willfully and materially breached the Merger Agreement with J&J;

(ii) that the Court find that Guidant breached the implied obligation of good faith and fair dealing; and

(iii) that the Court find that Boston Scientific and Abbott knowingly, intentionally and tortiously interfered with, and induced Guidant to breach, the Merger Agreement;

(iv) that after making such determinations, the Court award Plaintiff appropriate legal damages (general and special), in an amount to be determined at trial, but in no event less than $5.5 billion; and

(v) that the Court award such other necessary and proper relief, including, without limitation, attorneys' fees, interest, costs, as the Court may deem just and proper.

Dated: New York, New York
September 25, 2006

Kramer Levin Naftalis & Frankel LLP

By: _____
Harold P Weinberger (HW3240)
Timothy J. Helwick (TH5833)

1177 Avenue of the Americas
New York, New York 10036
Telephone: (212) 715-9000

Attorneys for Plaintiff Johnson & Johnson

JS 44
(Rev. 12/96)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I.(a) PLAINTIFF
Abbott Laboratories and Advanced Cardiovascular Systems, Inc.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANT
Johnson and Johnson, Inc. and Cordis Corporation

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED

(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER)
Frederick L. Cottrell, III
Anne Shea Gaza
Richards, Layton & Finger
One Rodney Square - P.O. Box 551
Wilmington, DE 19899
(302) 651-7700

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN X IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX (For Diversity Cases Only) FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business in Another State	☒ 5	☒ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

VI. ORIGIN (PLACE AN X IN ONE BOX ONLY)

☒ 1 Original Proceeding | ☐ 2 Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 50 Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgment

V. NATURE OF SUIT (PLACE AN X IN ONE BOX ONLY)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholder's Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Eject
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth In Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence
- Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVE
Action under patent laws for declaratory judgment, 35 u.s.c. §1 et seq.

VII. REQUESTED IN COMPLAINT: CHECK IF THIS IS A CLASS ACTION ☐ Under F.R.C.P. 23 DEMAND $ CHECK YES only if demanded in complaint: JURY DEMAND: X YES __ NO

VIII. RELATED CASE(S) (See instructions): IF ANY **Judge** Sue L. Robinson **Docket Numbers** 97-550, 98-314, 98-316, 98-80, 03-1138

DATE SIGNATURE OF ATTORNEY OF RECORD

September 29, 2006

FOR OFFICE USE ONLY
RECEIPT #_____ AMOUNT _____ APPLYING IFP_____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44
Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk

of Court for the purpose of initiating the civil docket sheet Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs - Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant If the plaintiff or defendant is a government agency use only the full name or standard abbreviations If the plaintiff or defendant is an official within a government agency identify first the agency and then the official giving both name and title

(b) County of Residence For each civil case filed, except U S plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing In U S plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved)

(c) Attorneys Enter firm name, address, telephone number, and attorney of record If there are several attorneys, list them on an attachment, noting in this section "(see attachment)"

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8 (a), F R C P , which requires that jurisdictions be shown in pleadings Place an "X" in one of the boxes If there is more than one basis of jurisdiction, precedence is given in the order shown below

United States plaintiff (1) Jurisdiction is based on 28 U S C 1345 and 1348 Suits by agencies and officers of the United States are included here

United States defendant (2) When the plaintiff is suing the United States, its officers or agencies, place an X in this box

Federal question (3) This refers to suits under 28 U S C 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States In cases where the U S is a party, the U S plaintiff or defendant code takes precedence, and box 1 or 2 should be marked

Diversity of citizenship (4) This refers to suits under 28 U S C 1332, where parties are citizens of different states When Box 4 is checked, the citizenship of the different parties must be checked (See Section III below; federal question actions take precedence over diversity cases)

III. **Residence (citizenship) of Principal Parties.** This section of the JS-44 is to be completed if diversity of citizenship was indicated above Mark this section for each principal party

IV **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause

V. **Nature of Suit** Place an "X" in the appropriate box If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit If the cause fits more than one nature of suit, select the most definitive

VI **Origin** Place an "X" in one of the seven boxes

Original Proceedings (1) Cases which originate in the United States district courts

Removed from State Court, (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U S C Section 1441 When the petition for removal is granted, check this box

Remanded from Appellate Court (3) Check this box for cases remanded to the district court for further action Use the date of remand as the filing date

Reinstated or Reopened (4) Check this box for cases reinstated or reopened in the district court Use the reopening date as the filing date

Transferred from Another District (5) For cases transferred under Title 28 U S C Section 1404(a) Do not use this for within district transfers or multidistrict litigation transfers

Multidistrict Litigation (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U S C Section 1407 When this box is checked, do not check (5) above

Appeal to District Judge from Magistrate Judgment (7) Check this box for an appeal from a magistrate's decision

VII. **Requested In Complaint** Class Action Place an "X" in this box if you are filing a class action under Rule 23, F R C P

Demand In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction

Jury Demand Check the appropriate box to indicate whether or not a jury is being demanded

VIII. **Related Cases.** This section of the JS-44 is used to reference relating pending cases if any If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases

Date and Attorney Signature. Date and sign the civil cover sheet
(rev 07/89)

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

06-613

Civil Action No. _____

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 4 COPIES OF AO FORM 85.

9-29-06
(Date forms issued)

(Signature of Party or their Representative)

Scott Rosenfield
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action